REMARKS

I. Claims Rejections under 35 U.S.C. § 103

A. Claims 1, 9 and 27-34 are Patentable over Omoigui in view of Muller.

Claims 1, 9 and 27-34 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Omoigui (U.S. 2004/0038874, "Omoigui") in view of Muller, *et al.* (U.S. 6,020,358 "Muller") (Office Action, page 3). Applicant respectfully disagrees.

In *KSR International Co. v. Teleflex Inc.*, the U.S. Supreme Court rejected the Federal Circuit's *rigid application* of the "teaching, suggestion, motivation" test ("the TSM test") in determining obviousness in the particular case in question. 127 L.Ed.2d 705, 82 U.S.P.Q.2d 1385, 1395 (2007) (emphasis added). According to the Supreme Court, the correct analysis is set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). *Id.* However, the *KSR* decision indicated that while the TSM test is not the sole method for determining obviousness, it may still be used and in some cases is helpful. *Id.* at 1396. ("When it first established [the TSM test], the Court...captured a helpful insight."). Indeed, the guidelines for the examination of patents in the wake of the *KSR* decision make clear that an Examiner may still apply the TSM test, after resolution of the *Graham* analysis. *See* Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57526, 57528 (Oct. 10, 2007) ("USPTO Guidelines").

The *Graham* factual inquiries are: (1) determine the scope and contents of the prior art; (2) ascertain the differences between the prior art and the claims at issue; (3) resolve the level of ordinary skill in the pertinent art; and (4) evaluate any evidence of secondary considerations. *KSR,* 82 U.S.P.Q.2d at 1395 (*citing Graham,* 383 U.S. at 15-17). Once the *Graham* factors have been addressed, the Examiner may apply the TSM test, asking whether (1) a teaching, suggestion or motivation exists in the prior art to combine the references cited, and (2) one skilled in the art would have a reasonable expectation of success. *See* USPTO Guidelines at 57534.

1. The *Graham* factual analysis.

The *Graham* factual inquiries begin with an analysis of the scope and content of the prior art, in view of the scope of the claimed invention. *See* USPTO Guidelines at 57527 (*citing Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005)). The instant claims recite, *inter alia*, methods of treating complex regional pain syndrome using a

specific compound, (+)-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione}. The prior art cited by the Examiner consists of Omoigui and Muller. Omoigui teaches that pain of all kinds may be treated by mediating the inflammatory response with any of hundreds or thousands of drugs that may impact inflammation. Omoigui does not teach or suggest (+)-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione}. Muller teaches that certain phenethylsulfones reduce the levels of TNF-α in a mammal. Muller does not disclose or suggest the use of (+)-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione} for treating complex regional pain syndrome as recited in the instant claims.

Regarding the differences between the prior art and the claims at issue, Applicant points out that the claimed invention is not described, taught or suggested by the references cited by the Examiner. The scope of the instant claims, which recite a specific compound, is in stark contrast with the breadth and general teachings of Omoigui and Muller, wherein hundreds if not thousands of compounds are described. The remarks below address these differences in detail, following the well-established case law concerning the obviousness of chemical compounds. *See Takeda Chemical Ind., Ltd. v. Alphapharm Pty., Ltd.*, 429 F.3d 1350 (Fed. Cir. 2007).[1]

2. The Examiner has failed to make a *prima facie* case of obviousness based on alleged structural similarity.

In the context of claims to chemical compounds and their biological properties, the Federal Circuit has recently applied the TSM test under 35 U.S.C. § 103. *See Takeda Chemical Ind., Ltd. v. Alphapharm Pty., Ltd.*, 429 F.3d 1350 (Fed. Cir. 2007). In *Takeda*, the Court held that the compounds at issue were not *prima facie* obvious over structurally similar "compound b" of the prior art because the prior art provided no motivation to modify compound b to arrive at the claimed compounds, and there was no reasonable expectation that the modification would provide the desired pharmacological properties. *Id.* at 1360. Indeed, the court noted that "we have cautioned 'that generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other.'" *Id.* at 1361 (*quoting In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir.

[1] Applicant asserts that the first and second *Graham* factors are of greatest importance in this case, however, Applicant reserves the right to later present arguments regarding the level of ordinary skill in the art and evidence of secondary considerations.

1985)). Thus, the current law of obviousness in cases concerning structurally similar compounds "requires a showing of 'adequate support in the prior art' for the change in structure." *Id.* at 1356 (*quoting In re Grabiak*, 769 F.2d at 729).

The instant claims are not obvious because the Examiner has not shown adequate support for the selection of the specific compound of the instant claims from the teachings of Omoigui and Muller. Omoigui teaches the treatment of pain of any type by mediating the inflammatory response with any of thousands or more drugs that may impact inflammation. This extremely broad teaching can hardly be said to focus on thalidomide derivatives as the Examiner suggests. (Office Action, page 6). But even if it did, Omoigui provides no teaching or suggestion of any particular thalidomide analogs, not to mention the specific compound of the instant claims. As was the case in *Takeda*, there is no showing of support for the change in structure from the compound of the prior art (in this case thalidomide), to the compound of the rejected claims. Thus, there is inadequate support in the prior art for the change in structure. *See Takeda*, 429 F.3d at 1356.

The Examiner alleges that because thalidomide and the compounds of Muller possess a phthalimide moiety, "it would be expected that each would have similar utility." (Office Action, page 5). The instant claims recite a single compound, (+)-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione}. This compound contains significant differences in structure as compared to thalidomide, regardless of the fact that the compounds each have a phthalimide group. Applicant respectfully points the Examiner to *Takeda*, in which the Court held that a change from a methyl group at the 6-position of a compound to an ethyl group at the 5-position was not *prima facie* obvious. *Id.* at 1359. Compared to *Takeda*, the structural changes required to arrive at (+)-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione} from thalidomide are much more drastic. One skilled in the art would be required to add an acetylamino group at one of four possible positions on the phthalimide group, and compeletely change the substitution at the 2-position. The references cited by the Examiner provide no guidance for these complex modifications. As the Court held in *Takeda*, the prior art cited by the Examiner does not provide a "finite number of identified, predictable solutions," but a "broad selection of compounds any of which could have been selected as the lead compound for further investigation." *Id.* at 1359. Therefore, there is inadequate support in the prior art for the change in structure to establish a *prima facie* case of obviousness. *Id.* at 1359.

Muller does not cure the defects of Omoigui. While Muller does disclose the racemic compound of the instant claims in Example 12, Muller provides no motivation to select this compound from the many examples provided therein for the treatment of complex regional pain syndrome. Furthermore, even assuming, *arguendo*, that one skilled in the art would select the compound of Example 12, the Examiner has provided no motivation to select the (+)-enantiomer of the compound. Whether a specific enantiomer has improved biologically activity or a more desirable pharmacological profile is recognized as unpredictable in the art. *See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d. 713, 754 (N.D. W. Va. 2004) (the prior art suggested unpredictability in the degree of activity exhibited by a specific enantiomer); *see also Ex Parte Bonfils*, 64 U.S.P.Q.2d 1456, 1461 (B.P.A.I. 2002).[2] Furthermore, it is well known to those skilled in the chemical and pharmaceutical arts that the separation and/or preparation of specific enantiomers is not predictable, nor are these processes always routine. *See, e.g.,* J. Darrow, "The Patentability of Enantiomers: Implications for the Pharmaceutical Industry," 2007 Stanford Tech. L. Rev. 2, ¶56 ("the process for making the racemate may not make obvious a process for resolving the racemate.") (copy enclosed). Thus, without specific guidance in the prior art, one skilled in the art would have no motivation to make or resolve the specific enantiomer of the instant claims without a specific teaching in the prior art. Without such motivation, a *prima facie* case of obvious cannot be made.

Finally, Muller provides no motivation to select the specific enantiomer of the instant claims for the treatment of complex regional pain syndrome. Indeed, Muller does not mention this specific disease at all. Therefore, in view of the current law of obviousness in cases of allegedly similar compounds, the Examiner has not provided adequate support in the prior art for the instant change in structure. *See Id.* at 1356. For these reasons alone, a *prima facie* case of obvious cannot be made.

3. One skilled in the art would have no motivation to combine the teachings of Omoigui and Muller to arrive at the methods of the instant claims.

The Examiner alleges that one skilled in the art would be motivated to combine Omoigui and Muller because "the references in combination teach or suggest each element of the instant claims...." (Office Action, page 5). Applicant disagrees.

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[2] *Bonfils* (copy enclosed) is a nonprecedential decision.

Mere "idenitification in the prior art of each component of [an invention] does not show that the combination as a whole...is obvious." *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006). Rather, "the law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention." *Id.* (Emphasis added). The Examiner's bare allegation that motivation to combine the cited references exists because Omoigui and Muller each disclose TNF-α inhibitors does not meet the legal requirement for a *prima facie* case of obviousness. (Office Action, page 5); *See Eli Lilly*, 471 F.3d at 1379. The Examiner has failed to show with specific facts how one skilled in the art would be motivated to combine the references to use one particular compound of Muller to treat one particular disease of Omoigui. Taken to its logical conclusion, the Examiner's rationale for motivation to combine the cited references would require that Omoigui in combination with Muller renders *prima facie* obvious the use of each compound disclosed by Muller for the treatment of every disease or disorder recited in Omoigui. Certainly this cannot be, and indeed is not, a correct application of the law of obviousness.

4. One skilled in the art would have no reasonable expectation of success to arrive at the instant claims in view of the teachings of Omoigui and Muller.

The Examiner alleges that one skilled in the art would have a reasonable expectatin of success, from the disclosure of Muller, to select (+)-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione} to treat complex regional pain merely because Omoigui teaches the use of TNF-α inhibitors to treat complex regional pain syndrome. (Office Action, page 4). Applicant disagrees.

To have a reasonable expectation of success, "one must be motivated to do more than merely 'vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave...no direction as to which of many possible choices is likely to be successful.'" *Medichem, S.A. v. Robaldo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (*quoting In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). Furthermore, the courts have long recognized the unpredictability of biological properties of chemical compounds. *See In re Eli Lilly & Co.*, 902 F.2d. 943, 948 (Fed. Cir. 1990) ("we recognize and give weight to the unpredictability of biological properties..."); *see also Takeda*, 429 F.3d at 1361.

The Examiner alleges that one skilled in the art would have a reasonable expectation of success because "the scope of Omoigui includes all compounds capable of

inhibiting or otherwise blocking the activity of TNF-α." (Office Action, page 4) (emphasis added). Even if, as the Examiner suggests, Omoigui teaches all compounds with TNF-α activity, one skilled in the art would be required to "try each of numerous possible choices until one possibly arrived at a successful result" with absolutely "no direction as to which of many possible choices is likely to be successful." *Medichem*, 437 F.3d at 1165. This is precisely what the courts have held not to be a reasonable expectation of success. *See Id.*; *O'Farrell*, 853 F.2d at 903-04.

Regarding the teachings of Muller, one skilled in the art would have no reasonable expectation that the selection of (+)-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione} from the many examples provided therein would be useful in treating complex regional pain syndrome. One skilled in the pharmaceutical arts understands the unpredictable nature of biological properties of chemical compounds and would not reasonably expect that every compound with TNF-α activity would be useful in treating complex regional pain syndrome. *See In re Eli Lilly & Co.*, 902 F.2d. at 948. This is especially so given that Muller does not teach the treatment of complex regional pain syndrome or the treatment of any type of pain at all.

Because the Examiner has not demonstrated that one skilled in the art would have had a reasonable expectation of success in practicing the methods of the instant claims by combining the teachings of Omoigui and Muller, the Examiner has failed to state a *prima facie* case of obviousness. Therefore, the instant claims are not obvious over Omoigui in view of Muller.

B. Claims 2-5 and 23 are Patentable over Omoigui in view of Muller and Merck.

Claims 2-5 and 23 stand rejected under 35 U.S.C. § 103(a) as unpatentable under Omoigui in view of Muller, further in view of Merck. (Office Action, page 6). The Examiner alleges that because Merck discloses that certain drugs, physical therapy and/or surgery can be used to treat complex regional pain syndrome, one skilled in the art would be motivated to combine this knowledge with the teachings of Omoigui and Muller, discussed above, to practice the methods of claims 2-5 and 23. (Office Action, pages 6-7). Applicant respectfully disagrees.

As discussed above, Omoigui in view of Muller does not teach or suggest the use of the specific compound as recited in instant claim 1 to treat complex regional pain syndrome. Merck does not cure this defect. Merck does not disclose or suggest anything

about (+)-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione} or its use in treating complex regional pain syndrome, much less a combination with another drug or therapy as claimed.

The Examiner has identified no teaching or suggestion that the recited compound may be used in treating pain, much less complex regional pain syndrome, much less the combination therapy. Nowhere does Muller or Merck suggest or motivate the use of the recited compound with an additional agent or therapy for treating pain, let alone complex regional pain syndrome. Thus, one of ordinary skill in the art would not have had a reasonable expectation of success from Omoigui, Muller and Merck. A *prima facie* case of obviousness has not been established and the rejection must be withdrawn.

II. Obviousness-Type Double Patenting Rejections

Claims 1, 9 and 27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over either claims 1, 6, 12 and 17 of U.S. Patent No. 6,020,358 ("the '358 patent"), or claims 1, 4, 10 and 15 of U.S. Patent No. 6,011,050 ("the '050 patent") in view of Omoigui. Applicant respectfully disagrees.

Obviousness-type double patenting is a judicially created doctrine intended to prevent improper timewise extension of the patent right by prohibiting the issuance of claims in a second patent which are not "patentably distinct" from the claims of a first patent. *See In re Braat*, 19 U.S.P.Q.2d 1289, 1291-92 (Fed. Cir. 1991). In *General Foods Corp. v. Studiengesellschaft Kohle mbH*, the Federal Circuit further explained that in an obviousness-type double patenting rejection "it is important to bear in mind that comparison can be made only with what invention is *claimed* in the earlier patent, paying careful attention to the rules of claim interpretation to determine what invention a claim *defines* and not looking to the claim for anything that happens to be mentioned in it as though it were a prior art reference." 23 U.S.P.Q.2d 1839, 1845 (Fed. Cir. 1992). Applicant respectfully submits that the Examiner is mistaken concerning what is claimed in the claims of the '358 and '050 patents, and by not considering what the claims of the the '358 and '050 patents define, the Patent Office arrives at a legally improper double patenting rejection of the claims.

The instant claims are drawn to methods for treating a specific disease—complex regional pain syndrome—using a specific compound. The claims of the '358 and '050 patents do not define the same invention of the instant claims. The claims of the '358 and

'050 patents merely recite methods of reducing undesirable levels of TNF-α in a mammal without any reference to complex regional pain syndrome. Furthermore, the claims of the the '358 and '050 patents provide no suggestion or motivation for one skilled in the art to select the specific compound from the broad genuses disclosed therein to treat the specific disease of the instant claims.

The Examiner cites *In re Petering* for the proposition that one may look to preferred embodiments to determine which compounds may be anticipated. (Office Action, page 11). First, Applicants point out that in a double patenting rejection, the claims, not the disclosure, of the cited patents must be used to support a rejection. *General Foods Corp.* 23 U.S.P.Q.2d at 1845. Second, Applicant points out to the Examiner that even the narrowest genuses of the claims of the '358 and '050 patents encompass hundreds of compounds– far greater than the 20 compound genus at issue in *Petering*.[3] The mere fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. MPEP § 2144.08; *In re Baird*, 16 F.3d 380, 382, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994); *see also In re Brouwer*, 77 F.3d 422, 425, 37 U.S.P.Q.2d 1663, 1666 (Fed. Cir. 1996)(the mere fact that one species selected from a genus could be modified or replaced to reach the claimed invention does not render the claims obvious unless the prior art suggested that modification or replacement)). Thus, because the specific compound of the instant claims is not obvious over the broad genuses of the claims of the '358 and '050 patents, the instant claims are patentably distinct from those claims.

The Examiner alleges that Omoigui discloses the treatment of pain using TNF-α inhibitors, and that complex regional pain syndrome is listed as a diease to be treated. (Office Action, page 10). While Omoigui does mention complex regional pain syndrome as one of many specific pain disorders, the Examiner has failed to demonstrate why one skilled in the art would select complex regional pain syndrome from the many diseases and disorders listed in Omoigui and apply that teaching to the claims of the '358 and '050 patents in order to arrive at the instant claims. Without demonstrating why one skilled in the art would be motivated to make this specific selection, the instant claims cannot be obvious over the claims of the '358 and '050 patents patent in view of Omoigui. *See*

[3] In this regard, Applicants point out that a genus of 259 members, for example, has been held to be sufficiently large to avoid anticipation of a species. (*In re Ruschig*, 343 F.2d 965, 974-75, 145 USPQ 274, 282 (Fed. Cir. 1965)(comparing a genus of 259 compounds to the 20 member genus in *Petering*)).

KSR, 82 U.S.P.Q.2d at 1395 (Examiner must "identify a reason that would have prompted a person of ordinary skill...to combine the elements in the way the claimed new invention does."). The claims of the '358 and '050 patents in view of Omoigui do not teach or suggest a method of treating the specific disease of the instant claims, much less doing so with the specific compound of the instant claims. For these reasons, the instant claims are patentably distinct from the claims of the '358 and '050 patents, and the double patenting rejection must be withdrawn.

Furthermore, the policy behind a double patenting rejection—the prevention of an unjustified extension of the term of a patent—does not support the Examiner's rejection in this case. *See In re Braat*, 19 U.S.P.Q.2d at 1291-92; *see also In re Kaplan*, 789 F.2d 1574, 1579 (Fed. Cir. 1986) ("the basis for...obviousness-type double patenting rejections is timewise extension of the patent right"). Allowance of the instant claims, directed to the treatment of complex regional pain syndrome with a specific compound, would not result in the timewise extension of the terms of the '358 and '050 patents. Therefore, Applicants respectfully request that the double patenting rejection be withdrawn.

In sum, Applicant respectfully submits that the rejection of the pending claims under obviousness-type double patenting should be withdrawn because no *prima facie* case of obviousness has been established for the pending claims over any of the claims of the cited patents. Applicant further submits that no terminal disclaimer over the cited patents is necessary.

Conclusion

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Please apply fees for a Request for Continued Examination ($810.00), and any other charges, or any credits, to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date: December 12, 2007

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Stanford Technology Law Review

The Patentability of Enantiomers: Implications for the Pharmaceutical Industry

JONATHAN J. DARROW*

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INTRODUCTION

A. The Pharmaceutical Industry

¶1 When it comes to sales figures, Big Pharma certainly lives up to its reputation. A recent study estimates worldwide pharmaceutical sales exceed $600 billion.[1] The United States is by far the single largest market for pharmaceutical products,[2] where companies invest hundreds of millions of dollars in drug discovery[3] and boast annual sales of $252 billion.[4]

¶2 What may come as more of a surprise is that a large portion of pharmaceutical sales is derived from a class of molecules called chiral molecules,[5] which have unique qualities that make them particularly interesting from a legal standpoint. The importance of chiral drugs cannot be overstated. Worldwide sales of chiral drugs reached more than $159 billion in 2002,[6] a figure which is expected to increase to over $200 billion by 2008.[7] In fact, chiral molecules comprise more than half the drugs approved worldwide,[8] including many of the world's top-selling drugs.[9] For example, Lipitor® and Zocor® (the world's first and fifth top selling drugs in 2005)[10] contain chiral molecules as the active pharmaceutical ingredient.[11] Other well-known chiral pharmaceuticals include ibuprofen, (sold under

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[1] Matthew Herper & Peter Kang, *The World's Ten Best-Selling Drugs*, FORBES.COM, Mar. 27, 2006, http://www.forbes.com/2006/03/21/pfizer-merck-amgen-cx_mh_pk_0321topdrugs.html. An estimate by the Organization for Economic Cooperation and Development places this figure in excess of $450 billion. ORG. FOR ECON. COOPERATION AND DEV., DRUG SPENDING IN OECD COUNTRIES UP BY NEARLY A THIRD SINCE 1998, ACCORDING TO NEW OECD DATA (Aug. 6, 2005), *available at* http://www.oecd.org/document/25/0,2340,en_2649_201185_34967193_1_1_1_1,00.html.

[2] Selena Class, *Pharma Overview*, CHEM. & ENG'G NEWS, Dec. 2, 2002, at 39, 39.

[3] Natalie A. Lissy, *Patentability of Chemical and Biotechnology Inventions: A Discrepancy in Standards*, 81 WASH. U. L.Q. 1069, 1069-70 (2003).

[4] Herper & Kang, *supra* note 1.

[5] Stephen C. Stinson, *Chiral Drugs*, CHEM. & ENG'G NEWS, Oct. 23, 2000, at 55, 55; Christopher J. Welch et al., *Preparative Chiral SFC as a Green Technology for Rapid Access to Enantiopurity in Pharmaceutical Process Research*, LC-GC EUROPE, May 2005, at 264, 264.

[6] A. Maureen Rouhi, *Chiral Business*, CHEM. & ENG'G NEWS, May 5, 2003, at 45, 46.

[7] Paul Moran, *New Ligands for Enantioselective Hydrogenation*, SPECIALTY CHEMS. MAGAZINE, July-Aug. 2003, at 16, 16.

[8] John Caldwell, *Do Single Enantiomers Have Something Special to Offer?*, HUMAN PSYCHOPHARMACOLOGY, Dec. 2001, at S67, S67 (reporting that 949 of 1675 drugs listed in the *Pharmacopoeia* are chiral); *Chiral Drugs Mark Signs of Maturity*, CHEM. BUS., Apr. 1998, at 31.

[9] Welch et al., *supra* note 5, at 264.

[10] Herper & Kang, *supra* note 1.

[11] Rouhi, *supra* note 6, at 46; Pfizer Inc. v. Ranbaxy Labs., 405 F. Supp. 2d 495, 500 (D. Del. 2005) (describing Lipitor® as "the largest selling pharmaceutical in history").

such a high level of similarity and predictability of structure, is an enantiomer even novel under § 102 if its mirror image has previously been disclosed?

¶7 These questions might appear to be purely academic, but nothing could be further from the truth. Although purified enantiomers exhibit identical physical and chemical properties (such as boiling point, density, and chemical reactivity) to their corresponding mirror images, they frequently exhibit very different biological activity.[25] This is because, just like a left-handed person who cannot use a right-handed baseball glove, one enantiomer may not fit into the active site of an enzyme where the other will. This means one enantiomer may have substantially different pharmacology and toxicology than the other enantiomer.[26] It also means pharmaceutical companies may want to market a drug containing only the more active enantiomer,[27] even if its mirror image has been disclosed or even previously patented. For a blockbuster drug based on a single enantiomer, the ability or inability to acquire a patent can significantly affect profitability by blocking the entrance of generic competitors.[28]

¶8 The differing activity of enantiomers has long been recognized in the pharmaceutical industry,[29] and by 1998 an entire generation of single-enantiomer drugs was already coming off patent.[30] Around the same time, it was predicted that single-enantiomer drugs would become the standard within the pharmaceutical industry.[31] This prediction is coming to pass. Lipitor® and Zocor®, mentioned above, are not only chiral, but are both single-enantiomer drugs.[32] Furthermore, a survey of 1200 drugs under development worldwide disclosed that 820 were chiral and, of those, 610 were being developed as single enantiomers.[33] The distinction between different enantiomers is so important that the Food and Drug Administration has issued a policy statement calling for single-enantiomer data during the approval process.[34]

¶9 Up to this point, the relevant inquiry has been framed in terms of the patentability of one enantiomer over its mirror image. In practice this is not usually the question presented. This is because when chiral molecules are synthesized in the laboratory—for example, in the preparation of pharmaceuticals—the two mirror image enantiomers are created in a fifty-fifty ratio called a racemic mixture, or racemate.[35] Due to the difficulty in separating the enantiomers from one another, many chiral drugs were initially sold in racemic form. As the patents covering these racemates expire, pharmaceutical companies naturally look to marketing the single-enantiomer versions of the drugs in order to extend product life and their market monopoly.[36] The question thus normally becomes not

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[25] FOOD AND DRUG ADMIN., FDA'S POLICY STATEMENT FOR THE DEVELOPMENT OF NEW STEREOISOMERIC DRUGS (1992), *available at* http://www. fda.gov/cder/guidance/stereo.htm; *see also* Caldwell, *supra* note 8, at S67 (noting that different stereoisomers have been reported to have different tastes and odors); GEOMETRIC ISOMERISM AND CHIRALITY: THE USAN PERSPECTIVE, *supra* note 16.

[26] Policy on Period of Marketing Exclusivity for Newly Approved Drug Products with Enantiomer Active Ingredients, 62 Fed. Reg. 2167 (Jan. 15, 1997).

[27] Strong, *supra* note 15, at 477 ("[E]ven though approximately 120 drugs currently in Phase III trials are racemates, most chiral compounds now in preclinical development are single enantiomers.").

[28] Hutt & Valentová, *supra* note 20, at 15.

[29] Caldwell, *supra* note 8, at S67 (reporting enantiomer studies from 1904 and 1908); Peter Mansfield et al., *Single-Enantiomer Drugs: Elegant Science, Disappointing Effects*, CLINICAL PHARMACOKINETICS, 2004, at 287, 287 ("Drug chirality has been researched . . . since . . . 1874.").

[30] *Chiral Drugs Show Signs of Maturity*, *supra* note 8, at 31.

[31] Patricia Van Arnum, *Chirals Spiral Upward*, CHEM. MARKETING REPORTER, Aug. 5, 1996, at SR27.

[32] Rouhi, *supra* note 6, at 46.

[33] *Chiral Drugs Show Signs of Maturity*, *supra* note 8, at 31.

[34] FDA'S POLICY STATEMENT FOR THE DEVELOPMENT OF NEW STEREOISOMERIC DRUGS, *supra* note 25; *Evolving Times Lead for Chiral Technology*, LABORATORYTALK.COM, June 18, 2003, http:// www.laboratorytalk.com news fro fro160.html.

[35] Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713 (N.D. W. Va. 2004). In contrast, naturally occurring compounds are often single enantiomers. Although the terms "racemic mixture" and "racemate" are frequently used interchangeably in the literature, they are not identical. For a discussion of terminology, see Alan G. Mitchell, *Racemic Drugs: Racemic Mixture, Racemic Compound, or Pseudoracemate*, J. PHARMACY PHARM. SCI., Jan.-Apr. 1998, at 8.

[36] Stephen C. Stinson, *Chiral Pharmaceuticals*, CHEM. & ENG'G NEWS, Oct. 1, 2001, at 79. This practice has been referred to as a "line extension" chiral switch. Caldwell, *supra* note 8, at S70.

the brand name Motrin®, and as over-the-counter versions Advil® and Nuprin®),[12] Claritin®, Allegra®,[13] Zoloft®, Paxil®,[14] Aleve®,[15] Prilosec® (and its racemic switch Nexium®), Prevacid®, Zyrtec®, Ritalin®, and even thalidomide.[16]

¶3 Like all inventions, the chiral compounds contained in pharmaceuticals must meet the statutory requirements of novelty, usefulness, and nonobviousness in order to be patentable.[17] Compounds exhibiting desirable pharmacological activity will generally meet the usefulness requirement. However, because of the economic importance and unique structural characteristics of chiral molecules, challenges to their patentability on the bases of novelty and nonobviousness have been asserted since as early as 1948.[18] With the explosive growth of the pharmaceutical industry—and particularly of chiral molecules[19]—over the last several decades, the patentability of chiral molecules has taken on increased significance[20] and remains a subject of litigation.[21]

¶4 This paper describes the legal framework surrounding the patentability of enantiomers (a subgroup of chiral molecules), identifies current questions and issues, and suggests how those issues should be resolved.

B. The Chemistry of Chiral Molecules

¶5 To understand the patentability of enantiomers, it is first necessary to understand their structure and characteristics. Chiral molecules exist in two distinct mirror image forms, called enantiomers.[22] Enantiomers are thus often likened to the right and the left hands, which are mirror images of each other, but which can not be superimposed upon each other.[23] Each enantiomer is therefore distinct from its counterpart. At the same time, knowledge of the structure of one enantiomer necessarily suggests the structure of the other. This observation motivates a fundamental inquiry: If one enantiomer is disclosed in the prior art, will its corresponding mirror image be unpatentable as obvious under § 103?

¶6 An isomer is one of a number of molecules that have the same molecular formula, but differ in the way the atoms are arranged. An enantiomer is a special type of isomer, in that it contains the same type and number of atoms as its mirror image, but the atoms are all connected in the same order.[24] The only structural difference between one enantiomer and the other is the geometry of the spatial arrangement of the atoms (here again, it is helpful to visualize the left and right hands). Given

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[12] *Chiral Drugs Show Signs of Maturity*, *supra* note 8, at 31.

[13] Class, *supra* note 2, at 40.

[14] *Do Single Stereoisomer Drugs Provide Value?*, THERAPEUTICS LETTER, June-Sept. 2002, *available at* http://www.ti.ubc.ca/PDF/45.pdf.

[15] Michael Strong, *FDA Policy and Regulation of Stereoisomers: Paradigm Shift and the Future of Safer, More Effective Drugs*, 54 FOOD & DRUG L.J. 463, 470 (1999).

[16] U.S. ADOPTED NAMES COUNCIL, GEOMETRIC ISOMERISM AND CHIRALITY: THE USAN PERSPECTIVE, *available at* http://www.ama-assn.org/ama/pub/category /15698.html (last visited Mar. 27, 2006). Thalidomide, infamous due to the birth defects that resulted after the drug was sold in the European market, is a special case because the two enantiomers interconvert at biologic pH. Although only one enantiomer is responsible for the birth defects, this interconvertability makes safe administration of the drug a challenge.

[17] 35 U.S.C. §§ 101-103 (2006).

[18] *In re* Williams, 171 F.2d 319 (C.C.P.A. 1948).

[19] Welch et al., *supra* note 5, at 264.

[20] Caldwell, *supra* note 8, at S69-S70 (arguing that when considering a chiral switch, "patent protection must be available for the single enantiomer"); A.J. Hutt & J. Valentová, *The Chiral Switch: The Development of Single Enantiomer Drugs from Racemates*, ACTA FACULTATIS PHARMACEUTICAE UNIVERSITATIS COMENIANAE, 2003, at 7 ("Over the last ten to fifteen years drug chirality, particularly the use of single enantiomers . . . has become an area of considerable interest."). Furthermore, the pharmaceutical industry is not the only one where single enantiomers are significant. The production of chiral compounds as single enantiomers is also a topic of ever-increasing importance in the chemicals industry. Kazuya Okano & Makoto Ueda, *Asymmetric Reduction Using Biocatalytic Reactions*, SPECIALTY CHEMS. MAGAZINE, Dec. 2004, at 40.

[21] *See, e.g.*, Pfizer Inc. v. Ranbaxy Labs., 405 F. Supp. 2d 495 (D. Del. 2005) (Lipitor®); Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713 (N.D. W. Va. 2004) (Levaquin®).

[22] JOHN MCMURRY, ORGANIC CHEMISTRY 287 (3d ed. 1992). Enantiomers are sometimes referred to as "optical isomers."

[23] *See, e.g.*, *Ortho-McN.*, 348 F. Supp. 2d at 720.

[24] *Ranbaxy*, 405 F. Supp. 2d at 503.

whether one enantiomer is patentable over its previously disclosed mirror image enantiomer, but whether the enantiomer is patentable over its previously disclosed racemate.

¶10 In addition to composition claims, United States patent law also provides for the patenting of processes.[37] As alluded to earlier, separating or "resolving" a racemate into its component parts is technically challenging. This is because each enantiomer has the same chemical (but not necessarily pharmacological) properties, and therefore traditional separation methods such as fractional distillation or chromatography may not work. Where the enantiomer as a composition is held to be nonpatentable over its racemate, would a new, useful, and nonobvious process for resolving the racemate be patentable? Even if the process is patentable, such a patent would not provide the right to exclude others from making and selling the product produced by that process. This is because there may be other, noninfringing processes that are capable of creating the same product. So perhaps a more important question is: If a racemate was disclosed long ago in the prior art, but a process to resolve the enantiomers has only recently been developed, can the enantiomer (as a compound) still be patented?

¶11 Many other questions remain as well. What if the same process has been used successfully on other racemates, but not on the one in question? Is it then obvious to combine the known racemate with the known resolution process? If so, does this mean that as more and more processes are developed and used on more and more racemates, it will become increasingly difficult to obtain patent protection for single-enantiomer drugs? In addition, many chiral molecules have more than one stereogenic center, resulting in not just two enantiomers, but in 2^{n-1} pairs of enantiomers (where n is the number of stereogenic centers). For chiral molecules with several stereogenic centers, does the potentially large number of candidate molecules make nonobvious the one that is pharmacologically most beneficial because there are more possibilities from which to choose?

C. Early Case Law

1. Enantiomers: Lack of Novelty?

¶12 The first time a United States court addressed the patentability of a single enantiomer seems be in the 1948 case *In re Williams*.[38] In *Williams*, the Board of Appeals rejected a claim to a single-enantiomer compound on the grounds of both lack of novelty and lack of invention.[39] The lack of novelty rejection was based on a prior art reference that disclosed the production of a compound having a formula identical to the claimed compound. Although the prior art compound was racemic, the reference did not so indicate. The Board of Appeals reasoned that because the enantiomer necessarily existed as part of the disclosed racemate, it could not be novel. The Court of Customs and Patent Appeals reversed, holding that "[t]he existence of a compound as an ingredient of another substance does not negative novelty in a claim to the pure compound, although it may, of course, render the claim unpatentable for lack of invention."[40] This rule that lack of novelty will not render an enantiomer unpatentable over its previously disclosed racemate has been consistently applied.[41]

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[37] 35 U.S.C. § 101 (2006).

[38] 171 F.2d 319 (C.C.P.A. 1948).

[39] Lack of invention is now called § 103 obviousness.

[40] *In re* Williams, 171 F.2d 319, 320 (C.C.P.A. 1948). The Court of Customs and Patent Appeals was the predecessor to the Court of Appeals for the Federal Circuit.

[41] *See, e.g.*, Pfizer Inc. v. Ranbaxy Labs., 405 F. Supp. 2d 495, 519 (D. Del. 2005) ("[C]ourts considering issues related to racemates and their individual isomers have concluded that a prior art disclosure of a racemate does not anticipate the individual isomers of the racemate . . . ."). The general rule of the Patent and Trademark Office is that, although "[a] genus does not always anticipate a claim to a species within the genus, . . . when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named."; *In re* May, 574 F.2d 1082, 1090 (C.C.P.A. 1978) ("The novelty of an optical isomer is not negated by the prior art disclosure of its racemate."); Brenner v. Ladd, 247 F. Supp. 51, 56 (D.D.C. 1965) ("[I]t should be noted that plaintiff's [enantiomer] is not considered by this court to be anticipated by the solution of [the racemate] disclosed in [the prior art]."; Sterling Drug Inc. v. Watson, 135 F. Supp. 173, 176 (D.D.C. 1955) ("[I]t matters not that [the enantiomer] in some form in combination may exist in nature, if it cannot be reduced to a form in which it can be used. It is this product which has been so reduced or resolved that it can be used that is here claimed."). MANUAL OF PATENT EXAMINING PROCEDURE § 2131.02 (8th ed. 2005) (Rev. 6, Sept. 2007).

¶13 To pharmaceutical companies, the novelty of enantiomers over their racemates is a favorable rule. As mentioned previously, many chiral drugs have historically been approved not as single enantiomers, but as racemates. Companies may be able to extend product life or even leverage a competitor's racemic product by making a chiral switch—an industry term for the development of a single-enantiomer drug when the drug in racemic form is already on the market.[42] For example, Sepracor, a Massachusetts company that markets the single-enantiomer drug Lunesta®, has obtained patents on single-enantiomer versions of sixteen chiral drugs previously sold as racemates by other firms.[43]

2. Enantiomers: Unpatentable as Obvious?

¶14 Although the novelty and usefulness requirements may easily be met by single enantiomers, the third and greatest hurdle remains: obviousness.[44] As the *Williams* court suggested in 1948, obviousness may render an enantiomer unpatentable over its previously disclosed racemate even where novelty will not. In *Williams*, a prior art reference disclosed the chemical formula of the racemate, and it was further asserted that the resolution of such a racemate was known to those skilled in the art. However, in holding the single enantiomer nonobvious and therefore upholding the patent, the court emphasized that no evidence was presented to establish that the compound was known to be racemic prior to the date of invention. Therefore, it was not shown that one skilled in the art would have any motivation to resolve it into its component enantiomers.[45]

¶15 From *Williams* it would appear that if a prior art reference discloses the chemical formula of the racemate, but does not disclose that it is racemic, the enantiomer will satisfy the nonobviousness requirement. This rule was limited, however, in the 1960 case of *In re Adamson*.[46] Like *Williams*, *Adamson* involved prior art references which disclosed the chemical formula of the claimed compound, but did not indicate its racemic nature. Another prior art reference, an organic chemistry text book by Karrer, did not specifically mention the claimed compounds, but did state that that synthetically produced organic compounds containing an asymmetric carbon atom are racemic. It also described several resolution methods, including the one used to resolve the claimed compound. The court held both the product and process claims invalid: "In view of the teachings of Karrer we feel that one of ordinary skill in the stereoisomer and pharmaceutical arts would recognize that the Adamson compounds exist as racemates, hence the fact that no reference to stereoisomerism is made by the Adamson references themselves is of no moment."[47] The court specifically distinguished *Williams* on the basis that neither Karrer nor an equivalent reference was cited in that case.

¶16 The Karrer text referred to in *Adamson* is frequently cited in the earlier cases addressing patentability of enantiomers, perhaps because it was one of the few works on stereoisomers available at that time. The stereoisomer arts have not remained static since their inception,[48] and *Adamson* could be read to suggest that as the state of the art advances it may be increasingly difficult to obtain a patent on a single-enantiomer molecule. As knowledge of enantiomers increases and resolution techniques improve, less inventive genius would be required to make a single enantiomer from its racemate. Indeed, such have been the advances in resolution techniques that last year in a patent

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example, there may be no known process for resolving the racemate. MPEP § 2121.02 (8th ed. 2003) ("Where a process for making the compound is not developed until after the date of invention, the mere naming of a compound in a reference, without more, cannot constitute a description of the compound.").

[42] Hurr & Valentová, *supra* note 20, at 15. Chiral switches are sometimes referred to as racemic switches.

[43] Stephen C. Stinson, *Counting on Chiral Drugs*, CHEM. & ENG'G NEWS, Sept. 21, 1998, at 83, 84.

[44] Song Huang, *The Nonobviousness Requirements for Biotechnological Inventions: Resolving Uncertainty in Favor of Innovation*, 21 SANTA CLARA COMPUTER & HIGH TECH. L.J. 597 (2005) (noting that obviousness is sometimes referred to as "the ultimate condition of patentability").

[45] *In re* Williams, 171 F.2d 319, 320 (C.C.P.A. 1948) ("[T]he idea of resolving it . . . would not occur to one skilled in the art.").

[46] *In re* Adamson, 275 F.2d 952 (C.C.P.A. 1960).

[47] *Id.* at 954.

[48] Caldwell, *supra* note 8, 870 (noting "recent technological advances that have [illegible]

dispute over blockbuster drug Lipitor®, the defendant "acknowledge[d] that one skilled in the art would know how to resolve racemates into their constituent enantiomers."[49]

I. MODERN DAY OBVIOUSNESS

A. Prima Facie Obviousness

¶17 It is not only that the stereoisomer arts have advanced significantly since *Adamson* was decided; so too have there been changes and refinements in the law of obviousness. The 1952 Patent Act introduced § 103, stating that "[a] patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."[50] From this seemingly simple concept—that one may not obtain a patent on something that is "obvious" in light of what already exists in the prior art—has evolved a rich and sometimes complex body of literature with respect to the chemical and pharmaceutical arts.

1. Graham v. John Deere Co.

¶18 It was not until 1966 that *Graham v. John Deere Co.* laid out the basic factors that set forth the current standard for making obviousness determinations.[51] The *Graham* Court noted that § 103 was a codification of the common law concept of "lack of invention" that dated back more than 100 years. The Court then explained: "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved."[52] Secondary considerations, sometimes called indicia of nonobviousness, are also relevant to the obviousness determination and include commercial success, long felt but unsolved need, and the failure of others.[53]

¶19 The *Graham* factors apply to obviousness determinations regardless of the art in question. While application of the *Graham* factors is well settled as the standard for making obviousness determinations, applying them to the chemical arts has in practice led to a large number of sometimes conflicting court opinions and generated confusion as to the proper determination of obviousness.[54]

2. Motivation or Suggestion to Combine

¶20 With respect to the first *Graham* factor (the scope and content of the prior art), "the relevant inquiry . . . is whether there is a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references."[55] Generally, this means

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[49] Pfizer Inc. v. Ranbaxy Labs., 405 F. Supp. 2d 495, 505 (D. Del. 2005).

[50] 35 U.S.C. § 103(a) (2006).

[51] 383 U.S. 1, 17-18 (1966).

[52] *Id.*

[53] *Id.* Secondary considerations *must* be considered before making an obviousness determination. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380 (Fed. Cir. 1986).

[54] *In re* Dillon, 919 F.2d 688, 700 (Fed. Cir. 1990) (Newman, J., dissenting) ("[t]he holdings of the prior law [regarding prima facie obviousness] were not entirely consistent"); *In re* Steinninsky, 444 F.2d 581, 585 (C.C.P.A. 1971) (acknowledging "this court's failure to render consistent precedent over the years"); Philippe Ducor, *Recombinant Products and Nonobviousness: A Typology*, 13 SANTA CLARA COMPUTER & HIGH TECH. L.J. 1, 17 (1997) ("The case law is very technical and sometimes conflicting"); William D. Marsillo, *How Chemical Nomenclature Confused the Courts*, 6 U. BALT. INTELL. PROP. L.J. 29, 31 (1997) (describing obviousness based on structural similarity as a "troublesome area of patent law."); *id.* at 34 ("Prima facie obviousness based on structural similarity between a claimed species and a prior art genus that includes the claimed species has proven to be a particularly difficult area for the courts to maintain a consistent jurisprudence.").

[55] Ruiz v. A.B. Chance Co., 234 F.3d 654, 664 (Fed. Cir. 2000); *In re* Mayne, 104 F.3d 1339, 1342 (Fed. Cir. 1997) ("When relying on numerous references or a modification of prior art, it is incumbent upon the examiner to identify some suggestion to combine references or make the modification."); *In re* Oehai, 71 F.3d 1565, 1570 (Fed. Cir. 1995) ("The mere chemical possibility that one of those prior art acids could be modified such that its use would lead to the particular cephem recited in claim 6 does not make the process recited in claim 6 obvious 'unless the prior art suggested the desirability of [such a] modification.'"); *In re* Jones, 958 F.2d 347, 351 (Fed. Cir. 1992) (stating that there must be some suggestion to combine, "either in the references themselves or in the knowledge generally available to one of ordinary skill in the art").

that to establish a prima facie case of obviousness, one must show "some objective teaching in the prior art or knowledge generally available to one of ordinary skill in the art that would lead that individual to combine the relevant teachings of the references."[56]

¶21 In the case of enantiomers, the references in question might include one that discloses a racemic compound and one or more others that describe resolution processes. As stated previously, it is well known in the art that enantiomers frequently exhibit different levels of activity from one another and that each enantiomer may not be equally responsible for side effects. Achieving higher pharmacological activity level at lower dosage levels and with fewer side effects will generally be desirable,[57] and it has been suggested in the literature that companies should attempt to separate enantiomers, assess the contribution of individual stereoisomers to the activity of interest, and select which stereoisomer to market.[58] Therefore, one skilled in the pharmaceutical arts would, at least in some cases, be motivated to combine a reference teaching a racemate with references indicating that single enantiomers may exhibit more desirable properties to attempt to isolate one or both enantiomers.

¶22 There is a second line of reasoning suggesting that sufficient motivation exists to resolve pharmaceutically-relevant racemates. In view of the extensive literature on the topic and single-enantiomer drugs already on the market or in development, one ordinarily skilled in the stereoisomer and pharmaceutical arts would be aware of the potential benefits of single-enantiomer molecules. The Federal Circuit has indicated that knowledge of persons ordinarily skilled in the art can serve as a source of motivation to combine references.[59] Furthermore, obviousness may be based on a single prior art reference where there is a suggestion to modify the teachings of that reference.[60] Therefore, motivation to isolate an enantiomer could potentially be found in a single reference disclosing the racemate.

¶23 Along these lines, one court found the prior art to provide "ample motivation to separate the optical isomers [of the racemate]."[61] The court stated that given "the development of synthesis methods via stereoselection and improvement in the analytical methods of optical isomers in the recent years, many came to believe that only one of the enantiomers is the important substance and that the other is . . . almost an impure substance."[62] Another court found that that the prior stereoisomer art as late as 1991 did not yet provide the requisite motivation to resolve racemates into their constituent enantiomers.[63] The court reasoned that resolution into component enantiomers could at best be expected to yield a two-fold increase in activity,[64] the benefit of which would be offset by the difficulty and complexity of the resolution process, as well as other drawbacks.[65]

¶24 While there may be some degree of tension between these two cases, it is important to remember that obviousness is a fact-specific inquiry. Care must be taken not to apply a general principle indiscriminately to specific circumstances. Simply because a racemate has been disclosed

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[56] *In re* Piasecki, 745 F.2d 1468 (Fed. Cir. 1984).

[57] Mansfield et al., *supra* note 29, at 287 ("[T]he most important motivation for developing enantiomers has been a genuine desire to improve efficacy and reduce adverse effects of drugs . . . .").

[58] Caldwell, *supra* note 8, at S69; Israel Agranat et al., *Putting Chirality to Work: The Strategy of Chiral Switches*, NATURE REVIEWS DRUG DISCOVERY, Oct. 2002, at 753, 755.

[59] *In re* Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

[60] *In re* Kotzab, 217 F.3d 1365, 1370 (Fed. Cir. 2000); JEROME ROSENSTOCK, THE LAW OF CHEMICAL AND PHARMACEUTICAL INVENTION, PATENT AND NONPATENT PROTECTION § 8.01[F] (2d ed. 1998) ("It is to be noted that a finding of obviousness in view of a single prior art reference is not unusual.").

[61] Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 752 (N.D. W. Va. 2004).

[62] *Id.*

Pfizer Inc. v. Ranbaxy Labs., 405 F. Supp. 2d 495, 517 (D. Del. 2005).

[64] Presumably, the two-fold limit is imposed by the fact that even if 100% of the activity level results from only one enantiomer, and the other is completely inactive, removing the inactive enantiomer will simply double the activity level per unit of compound. If both enantiomers are somewhat active, removing the less active one would increase the activity level by something less than 200%.

[65] *Ranbaxy*, 405 F. Supp. 2d at 517; *Mylan v. OrthoMcNeil*, 348 F. Supp. 2d at 747 (also noting that a two-fold difference in activity is the maximum possible difference in activity level between a racemate and its enantiomers).

does not necessarily mean that motivation exists to resolve it. For example, a reference disclosing a racemate might suggest that each enantiomer is equally responsible for side effects (or beneficial effects), that the enantiomers interconvert *in vivo*,[66] that the compound is pharmaceutically unsuitable (for example, due to toxicity or bioinstability), etc.

¶25 This type of disclosure in the prior art which actively discourages the claimed invention is said to "teach away" from the invention, and would make a finding of obviousness less likely.[67] Teaching away could also arise in the context of chiral molecules by a suggestion that a particular method of resolution should not work with a particular type of chiral molecule. If an inventor nevertheless combines that resolution method with the particular chiral molecule to resolve the racemate, the resulting enantiomer would more likely be held nonobvious.

3. Size of the Genus

¶26 Generally speaking, the larger the genus, the less likely that a species within that genus will be held obvious, and vice versa.[68] A "broad" genus, therefore, does not necessarily render obvious each compound within its scope.[69] It is not clear how many species a genus must contain before it can be considered "broad." Species have been held obvious over the disclosure of a genus containing 1200 compounds, where the prior art also disclosed that any member of the genus would have "desirable sodium and potassium eliminating properties."[70] At the other extreme, a genus containing 10^{36} members did not render a species claim obvious.[71] Unfortunately, the case law does not provide enough data points to determine at what point, if any, the size of the genus would be unlikely to render the species obvious.[72]

¶27 In some cases, a small genus can even anticipate (and not merely render obvious) a species, even if the species is not specifically named.[73] In *In re Petering*, a prior art reference disclosing a limited genus of twenty compounds rendered every species within the genus unpatentable.[74] The court emphasized, however, that it "is not the mere number of compounds . . . which is significant . . . but, rather, the total circumstances involved . . . ."[75]

¶28 In the case of enantiomers with one chiral center, the genus contains exactly two species, which is a very small genus.[76] Although size alone cannot support an obviousness rejection,[77] this factor weighs strongly in favor of obviousness.

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[66] Olivier Blin, *Separation des Enantiomers: Pour Quelle Amelioration du Rapport Benefice/Risque?*, THERAPIE, Nov.-Dec. 2004, at 625, 626.

[67] Alza Corp. v. Mylan Labs. Inc., 388 F. Supp. 2d 717, 738 (N.D. W. Va. 2005) ("A finding that a prior art reference 'teaches away' from combining references can alone defeat an obviousness claim.").

[68] ROSENSTOCK, *supra* note 60, at § 8.02[D] ("[W]here a genus or generic formula has a relatively small number of variables, that is, substituents, then a prima facie case of obviousness can be made out. One the other hand, where the genus or generic formula disclosed in the prior art has a relatively large number of substituents that can be made, a showing of obviousness is not so readily accomplished.").

[69] *In re* Baird, 16 F.3d 380, 382 (Fed. Cir. 1994); *In re* Jones, 958 F.2d 347, 350 (Fed. Cir. 1992) ("We decline to extract from *Merck* the rule that the Solicitor appears to suggest – that regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it . . . . Every case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts.").

[70] Merck & Co. v. Biocraft Labs., Inc., 874 F.2d 804, 807 (Fed. Cir. 1989).

[71] *In re* Bell, 991 F.2d 781, 784 (Fed. Cir. 1993); *see also In re* Baird, 16 F.3d at 383 (holding nonobvious three claimed species over a prior art genus of more than 100 million species).

[72] *See* Jeffery Fredman, *Are Oligonucleotide Primers and Probes Prima Facie Obvious Over Larger Prior Art Nucleic Acids?*, 19 SANTA CLARA COMPUTER & HIGH TECH. L.J. 285, 301 (2002) (discussing *In re Baird* and *In re Bell* and noting that the Federal Circuit, "when given cases where the genus was substantially larger [than the 1200-member genus of *Merck*], has stepped away from the bright line rule . . . that species are prima facie obvious where the genus was in the prior art.").

[73] Yeda v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006) (citing Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1380 (Fed. Cir. 2001)).

[74] *In re* Petering, 301 F.2d 676 (C.C.P.A. 1962).

[75] *Id.* at 681.

[76] Of course, as the number of chiral centers increases, so too does the size of the genus.

[77] Guidelines for the Examination of Claims Directed to Species of Chemical Compositions Based Upon a Single Prior Art Reference, 63 Fed. Reg. 47,090, 47,092 (Sept. 3, 1998).

4. Structural Similarity

¶29 In the chemical arts the *Graham* factors have been interpreted such that "a prima facie case of obviousness requires 'structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions.'"[78] Although both courts and commentators have indicated that structural similarity by itself has sometimes been held to provide the requisite motivation,[79] an examination of the cases cited reveals that the prior art in those cases disclosed something more than mere structural similarity. For example, in *In re May*, the prior art not only disclosed the racemate of the claimed enantiomer, but also suggested that the claimed enantiomer would possess one of the desired pharmaceutical properties.[80] In any event, the appellants in *May* conceded prima facie obviousness, so the court was not able to render a holding regarding the issue of prima facie obvious based on structure alone.[81] Similarly, in *In re Wilder*, the prior art disclosed not only a homologue of the claimed compound but also a similar process of manufacture and similar uses as those of the claimed compound.[82] Furthermore, the court did not separately address the issue of prima facie obviousness, focusing instead on whether or not Wilder had successfully overcome the prima facie showing.[83] Finally, in *In re Merck & Co.*, the prior art not only disclosed a similar compound but "expressly stated that [the claimed compound] was expected to resemble [the prior art compound] clinically in its depression alleviation effects."[84]

¶30 Nevertheless, in the case of enantiomers that are used as pharmaceuticals, structure "alone" is probably sufficient to create a prima facie case of obviousness in many cases. The Federal Circuit seems to accept this proposition.[85] More specifically, the prior art would satisfy the Federal Circuit's standard of prima facie obviousness that requires "structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions."[86] With a claimed enantiomer, the structurally similar prior art in question will frequently consist of a racemate that is already used as a pharmaceutical. There is always a motivation in the pharmaceutical industry to obtain products with improved properties.[87] Thus, as prior art, the pharmaceutically active racemate would provide both a nearly identical structure and the motivation to obtain the enantiomer.[88]

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[78] Yamanouchi Pharm. Co, v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000) (quoting *In re* Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)). *see In re* Soni, 54 F.3d 746, 750 (Fed. Cir. 1995) ("When a chemical composition is claimed, a prima facie case of obviousness under § 103 may be established by the PTO's citation of a reference to a similar composition, the presumption being that similar compositions have similar properties.").

[79] *See, e.g., In re* Mayne, 104 F.3d 1339, 1343 (Fed. Cir. 1997) ("Structural relationships often provide the requisite motivation"); *In re* Grabiak, 769 F.2d 729, 731 (Fed. Cir. 1985) ("When chemical compounds have 'very close' structural similarities and similar utilities, without more a prima facie case may be made.") (citing *In re* Wilder, 563 F.2d 457 (C.C.P.A. 1977) (adjacent homologs and structural isomers); *In re* May, 574 F.2d 1082, 1086 (C.C.P.A. 1978); and *In re* Hoch, 428 F.2d 1341 (C.C.P.A 1970) (acid and ethyl ester)); ROSENSTOCK, *supra* note 60, at § 8.02[A][1] (stating that "[t]he courts and the USPTO have indicated that a homologous series raises a prima facie case of obviousness," but citing older cases whose continued validity is questionable); Lissy, *supra* note 3, at 1080-81 ("Several cases have suggested that structural similarity alone may give rise to a prima facie case . . . [which result is only] consistent with *Dillon* if the state of knowledge in the field does in fact provide the motivation of likelihood of success.") (citing *In re* Merck & Co., 800 F.2d 1091, 1096 (Fed. Cir. 1986) and *In re* Payne, 606 F.2d 303, 313 (C.C.P.A. 1979) (pesticides which were neither true isomers nor homologues)); *see also In re* Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995) ("[A] known compound may suggest its analogs or isomers, either geometric isomers . . . or position isomers . . . .").

[80] *In re May*, 574 F.2d at 1086.

[81] *Id.* at 1089.

[82] *In re Wilder*, 563 F.2d at 459.

[83] *Id.* at 460.

[84] *In re* Merck & Co., 800 F.2d at 1096.

[85] *See, e.g., In re* Mayne, 104 F.3d 1339, 1343 (Fed. Cir. 1997) ("Structural relationships often provide the requisite motivation. . . ."); *In re* Dillon, 919 F.2d 688, 697 (Fed. Cir. 1990) ("The reference disclosed a lower homolog of the claimed compounds, so it was clear that impliedly a prima facie case existed.").

[86] Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000) (quoting *In re* Dillon, 919 F.2d at 692).

[87] *In re* Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995) ("[A] prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."). *See also* Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc., 777 F. Supp. 330, 353-54 (D. Del. 1991); *Yamanouchi*, 231 F.3d at 1341.

[88] *See* MPEP § 2144.09 (8th ed. 2001).

¶31 On the other hand, the Federal Circuit has stated that when a prima facie case of obviousness based on structural similarity is made, the presumption is that "similar compositions have similar properties."[89] As noted previously, similar properties cannot necessarily be presumed with respect to chiral molecules, since each enantiomer can exhibit significantly different *in vivo* behavior. However, the requirement is one of "similar" properties, not "identical" properties. Where a single enantiomer is used to treat the same condition as the racemate, this may be sufficient to constitute similar properties even if the efficacy is greater and side effects are fewer.

¶32 Regardless of how this issue is resolved, whether and when similar structure suggests similar properties is a two-edged sword for those attempting to demonstrate obviousness. On the one hand, asserting that similar structures can normally be expected to have similar properties might help to show that one skilled in the art would be motivated to make the new compound, and thus weigh in favor of obviousness. On the other hand, the same assertion could establish a baseline of expected properties against which to measure actual properties. If it can be shown that the newly discovered compound exhibits properties that are a substantial improvement over the prior art compound, this would tend to establish unexpected results and thereby rebut an obviousness showing.

5. Reasonable Expectation of Success

¶33 Motivation to combine references will be found only where there is a "reasonable expectation of success."[90] While the researcher cannot be certain that one enantiomer will be superior as to all relevant properties, absolute predictability is not required in order to reach the conclusion that an invention is obvious.[91] Furthermore, with respect to racemates there must be a reasonable expectation not only that the single enantiomer will exhibit desirable properties, but also that it will be possible to resolve the racemate in the first place.[92]

¶34 In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories Inc.*, the court held that under the "reasonable expectation of success" standard, the defendant had to prove that the prior art would not only motivate a person of ordinary skill in the art to make the enantiomer, but also reasonably suggest that the enantiomer would exhibit its "unique combination of properties."[93] The combination of properties of the enantiomer in question included double the potency, ten times greater solubility, and appreciably lower toxicity than the prior art.[94] Requiring this particular unique combination of properties is a relatively stringent standard, however, and should not be interpreted too strictly.[95] It would be nearly impossible for the prior art to suggest the "unique combination of

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necessarily considered equivalent by chemists skilled in the art and therefore are not *necessarily* suggestive of each other." (emphasis added)).

[89] In re *Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) ("When a chemical composition is claimed, a prima facie case of obviousness under § 103 may be established by the PTO's citation of a reference to a similar composition, the presumption being that similar compositions have similar properties."); *In re* Geiger, 815 F.2d 686, 688 (Fed. Cir. 1987) ("An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties."); *In re* Gyurik, 596 F.2d 1012, 1018 (C.C.P.A. 1979) ("In obviousness rejections based on close similarity in chemical structure, the necessary motivation to make a claimed compounds . . . rises from the expectation that compounds similar in structure will have similar properties."); *In re* May, 574 F.2d 1082, 1094 (C.C.P.A. 1978) ("[T]he basis of the prima facie case of obviousness, at least to a major extent, is based on the presumed expectation that compounds which are similar in structure will have similar properties.").

[90] Alza Corp. v. Mylan Labs. Inc., 388 F. Supp. 2d 717, 737 (N.D. W. Va. 2005) ("The inspiration to combine prior art references must also offer a 'reasonable expectation of success.'" (quoting *In re* O'Farrell, 853 F.2d 894, 904 (Fed. Cir. 1988)"); *see also* Pfizer Inc. v. Ranbaxy Labs., 405 F. Supp. 2d 495, 517 (D. Del. 2005) (finding that it may have been obvious "to try various salts in an attempt to find a salt with properties suitable for pharmaceutical use," but that there would not have been a reasonable expectation to success with calcium, a particular salt).

[91] *See, e.g.*, *In re* Longi, 759 F.2d 887, 896 (Fed. Cir. 1985) ("Only a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness."); *In re* Payne, 606 F.2d 303, 313 (C.C.P.A. 1979).

[92] *See* Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 752-53 (N.D. W. Va. 2004) (concluding that, as of 1984, the resolution of the particular enantiomers in question would have been a "logical extension of the prior art" though not "a routine matter").

[93] *Id.* at 749.

[94] *Id.* at 754.

[95] *See, e.g.*, *In re* Payne, 606 F.2d at 316 ("A finding of obviousness is not precluded . . . when only some, but not all, of the properties of a claimed compound are predictable from the prior art.").

properties" of a molecule that has not yet been isolated. It should be enough that the prior art provides a reasonable expectation that the enantiomer will possess at least one significantly improved property, as well as exhibit a combination of properties that would make the compound pharmaceutically acceptable.[96] Given the number of potential properties and the infinite possible magnitudes of each, anything more would impose a requirement of clairvoyance, not reasonable expectation.

¶35 To support its interpretation of "reasonable expectation of success," the *Ortho-McNeil* court cites *Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal, Inc.*, in which it was stated that "success was finding a compound that had high activity, few side effects, and lacked toxicity."[97] However, this statement must be viewed in context. In *Yamanouchi*, the party attempting to show "reasonable expectation of success" had merely demonstrated that an ordinary medicinal chemist would reasonably have expected the claimed compound to exhibit a baseline level of pharmacological activity. The *Yamanouchi* court noted that there were "tens of thousands" of compounds that exhibited this baseline level of activity, and that the claimed compound exhibited a level of activity 165 times greater than this in addition to having a desirable combination of pharmaceutical properties.[98]

¶36 Recall that reasonable expectation of success is a concept relevant to a showing of motivation to combine prior art references.[99] That is, without a reasonable expectation of success, one reasonably skilled in the art would have no motivation to combine references. Requiring a reasonable expectation of significant improvement in at least one property as well as an acceptable combination of other properties (not necessarily the particular combination of the claimed compound) would provide this motivation. Rather than requiring an expectation of the precise combination of properties possessed by the claimed invention, the *Yamanouchi* court was merely emphasizing that something more than an expectation of baseline activity was required in light of the fact that thousands of compounds would exhibit this property. Indeed, the case cited by *Yamanouchi* regarding reasonable expectation of success affirms that "[o]nly a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness."[100]

¶37 At the same time, one must be cautious to not set the bar for reasonable expectation of success too low. "'Obvious to try' has long been held not to constitute obviousness."[101] Thus one might argue that, absent any particular motivation provided by the prior art, isolating a single enantiomer would merely be "obvious to try" but would not necessarily render the single enantiomer obvious. As the Federal Circuit has noted, however, "the admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error,"[102] neither of which applies to enantiomers. The first is where "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful."[103] With a given racemate and its two enantiomers, there are at most two possible choices, not "numerous" or "many" possible choices.

¶38 The second main category of error where an invention that is obvious to try might nevertheless be held nonobvious is where the prior art suggests exploring a new technology or general approach but gives "only general guidance as to the particular form of the claimed invention or how to achieve

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[96] *In re* Dillon, 919 F.2d 688, 693 (Fed. Cir. 1990) ("[T]he statement that a prima facie obviousness rejection is not supported if no reference shows or suggests the newly-discovered properties and results of a claimed structure is not the law.").

[97] 231 F.3d 1339, 1345 (Fed. Cir. 2000).

[98] *Id.*

[99] Alza Corp. v. Mylan Labs. Inc., 388 F. Supp. 2d 717, 737 (N.D.W. Va. 2005).

[100] *In re* Longi, 759 F.2d 887, 897 (Fed. Cir. 1985).

[101] *In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988).

[102] *Id.*

[103] *Id.*

it."[104] In the case of enantiomers, one of two precise compounds is suggested by a given prior art racemate. Those skilled in the art need not consider which combinations of substituents are likely to produce compounds with desirable properties. While the process necessary to resolve a given racemate may not be obvious, it can hardly be said that the mere selection of an enantiomer in light of its known racemate constitutes innovation exceeding the abilities of one ordinarily skilled in the art. Indeed, it is not inconceivable that an employee in the marketing department of a pharmaceutical company might suggest a chiral switch.

6. Conclusion as to Prima Facie Obviousness

¶39 It is tempting to conclude based on the above discussion that enantiomers will generally be held prima facie obvious over their previously disclosed racemates or their enantiomers of opposite rotation. The chemical structure of each enantiomer is nearly identical, a disclosed racemate is a genus that contains only two species, there is ample suggestion in the pharmaceutical arts to generally motivate the resolution of pharmaceutically relevant racemates, and in light of recent advances in resolution techniques there is an increased likelihood of success in obtaining a selected enantiomer.

¶40 In fact, a number of courts have ruled consistently with this line of reasoning. In 1997, the U.S. District Court for the Northern District of Georgia stated in dicta that "disclosure of the racemate or racemic mixture makes prima facie obvious the separate enantiomers of that racemate."[105] Nor was the Georgia court breaking new ground in its determination. More than thirty years earlier, the District Court for the District of Columbia arrived at this same conclusion: "[I]n the absence of unexpected or unobvious beneficial properties, an optically active isomer [i.e., an enantiomer] is unpatentable over either the isomer of opposite rotation or, as in this case, the racemic compound itself."[106] As of 1969, this principle was apparently so well established that one appellant did not even contest prima facie obviousness, conceding that "under existing law a [stereoisomer] is not patentable over its known racemic mixture unless it possesses unexpected properties not possessed by the racemic mixture."[107] In 1992, the Federal Circuit acknowledged these and other cases by stating in dicta that "[p]articular types or categories of structural similarity without more have, in past cases, given rise to prima facie obviousness,"[108] and reaffirmed this position in 1995 when it stated that, "[w]hen a chemical composition is claimed, a prima facie case of obviousness under §103 may be established by the PTO's citation of a reference to a similar composition, the presumption being that similar compositions have similar properties."[109]

¶41 However, it would be a mistake to conclude that under the current state of the law an enantiomer will in all cases be prima facie obvious over either its mirror image enantiomer or its racemate. Indeed, the Federal Circuit has stated that "generalization is to be avoided insofar as specific structures are alleged to be prima facie obvious one from the other."[110] Citing this and other statements of the Federal Circuit, the District Court for the Northern District of West Virginia recently refused to accept the assertion that an enantiomer was prima facie obvious vis-à-vis its racemate.[111] And in a 2002 non-precedential decision, the Board of Patent Appeals and Interferences

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[104] *Id.*

[105] Emory Univ. v. Glaxo Wellcome Inc., 44 U.S.P.Q.2d 1407, 1414 (N.D. Ga. 1997) (but also noting that "if the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public").

[106] Brenner v. Ladd, 247 F. Supp. 51, 56 (D.D.C. 1965); *see also* Sterling Drug, Inc. v. Watson, 135 F.Supp. 173 (D.D.C. 1955) (holding an otherwise obvious enantiomer nevertheless patentable over its racemate based on unexpected results, failure of others, and commercial success).

[107] *In re* Anthony, 414 F. 2d 1383 (C.C.P.A. 1969).

[108] *In re* Jones, 958 F.2d 347, 349-50 (Fed. Cir. 1992). *See also In re* Grabiak, 769 F.2d 729, 731 (Fed. Cir. 1985) ("When chemical compounds have 'very close' structural similarities and similar utilities, without more a prima facie case may be made.").

[109] *In re* Soni, 54 F.3d 746, 750 (Fed. Cir. 1995). *In re* Dillon, 919 F.2d 688, 698 (Fed. Cir. 1990) ("similar properties may normally be presumed when compounds are very close in structure").

[110] *In re Jones*, 958 F.2d at 350 (citing *In re* Grabiak, 769 F.2d at 731); *see also In re* Lancer, 465 F.2d 896, 899 (C.C.P.A. 1972) ("Homology should not be automatically equated with prima facie obviousness . . . .").

[111] Ortho McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 749 n.29 (N.D. W. Va. 2004).

noted that the disclosure of one enantiomer does not necessarily create a prima facie case of obviousness as to the other enantiomer.[112]

¶42 Whether or not an enantiomer is prima facie obvious in light of its racemate may well turn on the definitions of "reasonable expectation" and "success," neither of which has yet been defined with precision. Success should require at a minimum that the single enantiomer be superior to the racemate in some way. If it were not superior in any way, what motivation would the intensely practical researcher have to resolve the racemate?[113] The courts have unequivocally stated that reasonable expectation requires something less than absolute predictability, but how much less is not clear. Should reasonable expectation require a greater than 50% probability of success (similar to the preponderance of the evidence standard)? Or simply that the probability of success be more than negligible (the inverse of the beyond reasonable doubt standard)?

B. Overcoming Obviousness

1. Obviousness and Prima Facie Obviousness Distinguished

¶43 Prima facie obviousness must not, of course, be confused with the ultimate determination of obviousness. In holding that no prima facie case of obviousness had been established, the *Ortho-McNeil* court noted that *Graham* findings must be made to establish a prima facie case of obviousness.[114] The first case cited by the *Ortho-McNeil* court, *In re Mayne*, states that *Graham* factors are the foundational facts in the prima facie determination, that secondary considerations "are relevant to the determination of obviousness," and that "each obviousness determination rests on its own facts."[115] It is important to note that these latter two quotations refer to *obviousness*, not prima facie obviousness. Similarly, the portion of *A.B. Chance* cited by *Ortho-McNeil* refers to obviousness, not prima facie obviousness.[116] *A.B. Chance* later notes that secondary considerations may be sufficient to *overcome* a prima facie case of obviousness.[117] Thus, while courts sometimes refer to "the four *Graham* factors,"[118] it is only the first three *Graham* factors that are considered when making a prima facie obviousness determination.[119, 120]

¶44 Prima facie obviousness is a procedural tool, used to shift the burden of proof to the applicant.[121] That is, once a showing of prima facie obviousness is made, the applicant then has the opportunity to rebut (and bears the burden of rebutting) this prima facie showing. Therefore, even if a court determines that an enantiomer is prima facie obvious over its racemate, it may still be nonobvious and therefore patentable if the presumption of obviousness can be overcome.

¶45 There is no question that the ultimate determination of obviousness must rest on more than structure alone. It is frequently noted that that "[f]rom the standpoint of patent law, a compound and all of its properties are inseparable . . . ."[122] Thus in the determination of obviousness courts must

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[112] *Ex parte* Bonfils, 64 U.S.P.Q.2d (BNA) 1456, at *15-16 (B.P.A.I. 2002).

[113] *See In re* Stemniski, 444 F.2d 581, 586 (C.C.P.A. 1971). Note that this in effect imposes a higher standard than does the § 101 utility requirement, under which an invention may be patentable even if it is no better than, or in fact not as good as, existing products.

[114] *Ortho-McNeil*, 348 F. Supp. 2d at 749 n.19.

[115] *In re* Mayne, 104 F.3d 1339, 1341 (Fed. Cir. 1997).

[116] Ruiz v. A.B. Chance Co., 234 F.3d 654, 663 (Fed. Cir. 2000).

[117] *Id.* at 667.

[118] *See, e.g.*, Richardson-Vicks, Inc. v. Upjohn Co., 122 F.3d 1476, 1480 (Fed. Cir. 1997); Emergency Fuel, LLC v. Pennzoil-Quaker State Co., 293 F. Supp. 2d 569, 585 n.23 (D. Md. 2003).

[119] Guidelines for the Examination of Claims Directed to Species of Chemical Compositions Based Upon a Single Prior Art Reference, 63 Fed. Reg. 47,000, 47,002 (Sept. 3, 1998) (noting that, in establishing a prima facie obviousness case, office personnel should make findings as to the first three *Graham* factors).

[120] It should be noted that the *Ortho-McNeil* court does in fact base its conclusion of prima facie obviousness on the first three *Graham* factors.

[121] *In re* Piasecki, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984) ("The concept of *prima facie* obviousness . . . is but a procedural mechanism . . . ."); Ducor, *supra* note 54, at 15.

[122] *In re* Papesch, 315 F.2d 381, 391 (C.C.P.A. 1963).

consider not only structure, but also properties.[123] However, this statement goes not to the prima facie determination of obviousness, but to the ultimate determination.[124] More generally, the Federal Circuit has stated that "reliance on *per se* rules of obviousness is legally incorrect and must cease."[125]

2. Unexpected Results

¶46 One way to overcome a prima facie case of obviousness is to show that the enantiomer "exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected" despite the disclosures of the prior art.[126] Thus, if an enantiomer exhibits one or more properties which are superior to and unexpected in light of the known properties of the racemate, the enantiomer may be patentable despite a high degree of structural similarity. Looked at another way, unexpected results can show that a claimed compound that appeared to be obvious on structural grounds was not obvious when looked at as a whole.[127] This is a sensible exception to the obviousness standard, for the simple reason that "that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious."[128]

¶47 Where a given pharmaceutical is already being marketed as a racemic mixture, the most likely difference between the racemate and the enantiomer may be the level of pharmacological activity. An increased efficacy level can, at least in some cases, constitute an "unexpected result."[129] However, "since structurally similar compounds generally have similar properties, an unexpected result must be a substantial improvement over the prior art."[130] Recently, *Ortho-McNeil* held that it would not have been expected that an enantiomer would be "twice as potent, about ten times more soluble, and appreciably less toxic" than its racemate.[131] It emphasized that, even if the prior art suggested improvements in one or two properties of the enantiomer over the racemate, the *combination* of improved properties was unexpected.[132] However, improvements in multiple properties are not necessary to rebut obviousness; significant improvement in one of a spectrum of common properties can be sufficient.[133]

¶48 What constitutes "significant improvement" in one property? Is there a minimum multiple of increased potency that is required before "significant improvement" will be found? It appears that the answer is no, and that the relevant inquiry is rather whether the prior art suggested the degree of

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[123] Eli Lilly & Co. v. Zenith Goldline Pharma., Inc., 2001 WL 1397304, at *6 (S.D. Ind. Oct. 29, 2001) ("Obviousness cannot be determined by chemical structure alone.").

[124] *In re* Dillon, 919 F.2d 688, 697 (Fed. Cir. 1990) ("Properties, therefore, *are* relevant to the creation of a *prima facie* case in the sense of affecting the motivation of a researcher to make compounds closely related to or suggested by a prior art compound, but it is not required, as stated in the dissent, that the prior art disclose or suggest the properties newly-discovered by an applicant in order for there to be a *prima facie* case of obviousness. . . . *Papesch,* however, did not deal with the requirements for establishing a *prima facie* case. . . ." (emphasis in original)).

[125] *In re* Ochiai, 71 F.3d 1565 (Fed. Cir. 1995). The Patent Office has adopted this position. MPEP § 2144.08 (8th ed. 2003) ("Use of per se rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 U.S.C. 103." (citing *In re* Brouwer, 77 F.3d 422, 425 (Fed. Cir. 1996), *In re Ochiai*, 71 F.3d at 1572, and *In re* Baird, 16 F.3d 380, 382, (Fed. Cir. 1994))).

[126] *In re* Soni, 54 F.3d 746, 750 (Fed. Cir. 1995) (noting that "[t]he principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results"); Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 749 (N.D. W. Va. 2004); *In re Dillon*, 919 F.2d at 692 (en banc) (rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties).

[127] *See, e.g., In re* Papesch, 315 F.2d 381, 391 (1963).

[128] *In re Soni*, 54 F.3d at 750.

[129] *In re* Chupp, 816 F.2d 643, 646 (Fed. Cir. 1987); U.S. v. Ciba-Geigy Corp., 508 F. Supp. 1157, 1169 (D. N.J. 1979) (Ten times greater potency resulted in "a significant enough [difference] to be deserving of a patent"); *In re* Wiechert, 370 F.2d 927, 932 (C.C.P.A. 1967) ("In the case at bar, we are impressed by the 7-fold improvements in activity and, in the absence of valid countervailing evidence, we find the claimed compounds to be unobvious.").

[130] Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 749 (N.D. W. Va. 2004).

[131] *Id.* at 754-55.

[132] *Id.* at 754 (the enantiomer "represents the unusual case in which each of its desired properties is superior to . . . those of [the racemate].").

[133] *Ortho-McNeil*, 348 F. Supp. 2d at 754 (even absent the combination of improved properties, a skilled artisan could not even have expected that the enantiomer would be twice as potent as the racemate); *In re Chupp*, 816 F.2d at 646 (evidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a prima facie case of obviousness).

improvement that is exhibited in the claimed compound.[134] In *In re Carabateas*, the prior art suggested at most a four to eight-fold increase in activity level, whereas the applicant's compound exhibited a nineteen-fold increase.[135] In a concurring opinion, Judge Rich suggested that it was the difference between the expected improvement and the observed improvement that should be controlling.[136] That is, merely because the new compound exhibits a (seemingly large) nineteen-fold increase, this will only be evidence of nonobviousness if the prior art suggested something substantially less than a nineteen-fold increase.

¶49 Exactly how much less is not clear. In *Ortho-McNeil*, the court found that a mere two-fold increase was unexpected, even in light of a prior art showing that some increase might be expected.[137] In *In re Soni*, the Federal Circuit seemed to adopt the principle that prima facie obviousness can be overcome by demonstrating substantially improved results over what the prior art would have suggested.[138] However, it then muddled the legal standard by holding that, "when an applicant demonstrates *substantially* improved results . . . and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary."[139] As the dissent pointed out, this holding appears to remove the requirement that a showing be made as to the particular level of activity suggested by the prior art, and then compare *that* level of activity to the observed level.[140] In other words, when establishing unexpected results, it should not be enough to merely show that the claimed compound exhibited a substantially higher level of activity than prior art compound. It must be a substantial improvement *over the improvement that was suggested by the prior art.*

¶50 The properties of chemical compounds *in vivo* are generally considered to be unpredictable.[141] Specifically with respect to stereoisomers, it is well known that different enantiomers of the same chiral compound can have very different pharmacological properties.[142] It has been suggested that the difficulty in predicting the pharmacological properties of racemates and their enantiomers may result in therapeutically useful compounds being overlooked.[143] Even if one enantiomer is known to possess a desired property, the other enantiomer could be completely inactive, have some activity, be an antagonist as to its mirror image, or have separate but desirable activity.[144] If it is difficult to

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[134] *In re* Soni, 54 F.3d 746, 751 (Fed. Cir. 1995).

[135] *In re* Carabateas, 357 F.2d 998, 1001 (C.C.P.A. 1966) (Rich, J., concurring).

[136] *Id.* at 1001 ("[T]he art makes no suggestion whatever that a reversal of the ester linkage would result in an increased activity approximately the nineteen-fold increase found by appellant. At the very best, the art suggests an increase of the order of four to eight times . . . . The question is not, it seems to me, whether the art suggests an improvement, but rather whether it reasonably suggests the particular improvement relied upon for patentability in both its qualitative and quantitative sense.").

[137] Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 749 (N.D. W. Va. 2004). This finding is perhaps not surprising since a two-fold increase is the maximum increase possible for one enantiomer over its racemate.

[138] *In re Soni*, 54 F.3d at 750-51.

[139] *Id.* at 751 (Fed. Cir. 1995) (emphasis added).

[140] *Id.* at 754 (Fed. Cir. 1995) (Michel, C.J., dissenting) ("Neither the specification nor any post-rejection submission contains objective evidence tending to establish either (1) a baseline of expected improvements against which to measure the observed improvements, or (2) the lack of any such baseline expectation in the relevant prior art, as a result of which all degrees of improvement would be unexpected.").

[141] Ducor, *supra* note 54, at 16; Glastetter v. Novartis Pharm. Corp., 252 F.3d 986, 990 (8th Cir. 2001) ("Even minor deviations in molecular structure can radically change a particular substance's properties and propensities."); 2 DONALD S. CHISUM, CHISUM ON PATENTS § 5.04[6] at 5-429 (2000) ("Because of the unpredictable nature of chemical reactions, a newly-synthesized compound may be very similar in structure to known and existing compounds and yet exhibit very different properties."); Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 2001 WL 1397304 (S.D. Ind. Oct. 29, 2001) ("The unpredictable nature of chemical reactions is especially pronounced, of course, when dealing with medicinal chemistry, where the biological effects of chemical reactions may be exceedingly difficult to predict from the chemical structure of a compound.").

[142] Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 754 (N.D. W. Va. 2004) ("Of course . . . the prior art suggests that one of the enantiomers is often more active and soluble than its racemate. . . . [T]he prior art certainly indicates that one enantiomer is often more therapeutically active than the other. . . ."); Charlie Lasherness, *Patent Reissue Census Claims*, 26 T. JEFFERSON L. REV. 85, 87-88 (2003) ("[D]ifferent enantiomers of the same chiral compound can have very different pharmacological properties."); MURRY, *supra* note 22, at 323 ("[D]ifferent stereoisomers have . . . dramatically different biological properties.").

[143] Hutt & Valentovic, *supra* note 20, at 14-15 ("[I]t is possible that therapeutically useful compounds may have been lost as the racemates were evaluated and thought to be unsuitable for development, whereas their individual enantiomers may have had pharmacologically useful properties.").

[144] Agranat et al., *supra* note 58, at 754.

predict the *in vivo* properties of a hypothetical compound, then an observed property of that compound once it is created may be more likely to be unexpected.

¶51 On the other hand, it is generally accepted that one optical isomer will typically have much higher activity than the other, so that superior activity for at least one of the isomers as compared to the racemate is to be expected.[145] It has therefore been held that differential physiologic activity from one enantiomer to another is not, by itself, unexpected,[146] but that a particular combination of properties may be unexpected.[147]

3. Secondary Considerations

¶52 If the improved properties of an enantiomer do not rise to the level of unexpectedness, a second avenue for challenging prima facie obviousness is to show the presence of secondary considerations. Secondary considerations, also known as indicia of nonobviousness, "must be considered in determining obviousness."[148] Indeed, such objective indicia may be "the most probative and cogent evidence in the record"[149] and "alone may defeat a claim of obviousness."[150] Secondary considerations considered by courts to suggest nonobviousness include commercial success,[151] long-felt need,[152] failure of others,[153] copying by competitors,[154] praise by others/industry recognition,[155] industry acquiescence,[156] skepticism by those in the art, and licensing by others. Near simultaneous invention weighs in favor of obviousness.[157]

¶53 Commercial success and copying by competitors will almost always weigh in favor of the pharmaceutical patent holder. To establish commercial success, the patentee must merely show significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent.[158] Once this showing is made, it is presumed that the commercial success is due to the patented invention, and the burden then shifts to the other party to show that commercial success is due to other factors.[159]

¶54 Normally, a generic company would not challenge a single-enantiomer patent held by a brand name manufacturer unless it wanted to copy the single-enantiomer drug. Not only would the copying itself suggest nonobviousness, but it might also suggest commercial success, a second factor weighing in favor of nonobviousness.[160] Those seeking to invalidate patents on the basis of obviousness have frequently asserted that commercial success is the result of marketing strategy and not the efficacy of the product.[161] This assertion is supported by the analysis of the Therapeutics Initiative of the

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[145] Carlos M. Correa, *Public Health and Patent Legislation in Developing Countries*, 3 TUL. J. TECH. & INTELL. PROP. 1, 32 (2001).

[146] *In re* Adamson, 275 F.2d 952, 955 (C.C.P.A. 1960).

[147] Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 348 F. Supp. 2d 713, 755 (N.D. W.Va. 2004) ("Although the prior art suggests that [the enantiomer's] relatively higher activity and lower toxicity were not surprising in themselves, the combination of those properties would have been unexpected.").

[148] Ruiz v. A.B. Chance Co., 234 F.3d 654, 667 (Fed. Cir. 2000).

[149] Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538 (Fed. Cir. 1983).

[150] *Ortho-McNeil*, 348 F. Supp. 2d at 749; *but see* Newell Co. v. Kennedy Mfg. Co., 864 F.2d 757, 768-69 (Fed. Cir. 1988) (stating that "although these factors must be considered, they do not control the obviousness conclusion").

[151] *In re* Piasecki, 745 F.2d 1468, 1473, (Fed. Cir. 1984); Sterling Drug Inc. v. Watson, 135 F. Supp. 173 (D.D.C. 1955).

[152] Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1539 (Fed. Cir. 1983); *In re* May, 574 F.2d 1082, 1092 (C.C.P.A. 1978).

[153] Sterling Drug Inc. v. Watson, 135 F. Supp. 173 (D.D.C. 1955).

[154] Rebuttal evidence may include evidence that the claimed invention was copied by others. *See, e.g., In re* GPAC, 57 F.3d 1573, 1580 (Fed. Cir. 1995); Hybritech Inc. v. Monoclonal Antibodies, 802 F.2d 1367, 1380 (Fed. Cir. 1986).

[155] Brenner v. Ladd, 247 F. Supp. 51 (D.D.C. 1965).

[156] Eli Lilly & Co. v. Generix, 324 F. Supp. 715, 718 (S.D. Fla. 1971), *aff'd* 460 F.2d 1096 (5th Cir. 1972).

[157] Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 753 & 757-58 (N.D. W. Va. 2004).

[158] Alza Corp. v. Mylan Labs. Inc., 388 F. Supp.2d 717, 740 (N.D. W. Va. 2005) citing J.T. Eaton & Co. Inc., v. Atlantic Paste & Glue Co., 106 F.3d 1563, 1571 (Fed. Cir. 1997); (holding the claimed invention obvious in spite of a finding of "at least moderate commercial success").

[159] *Id.*

[160] Pfizer Inc. v. Ranbaxy Labs., 405 F. Supp. 2d 495, 518 (D. Del. 2005); "Indeed, the fact that Ranbaxy has chosen to copy Lipitor . . . further demonstrates the success . . . of Lipitor.'".

[161] *Id.*

University of British Columbia. After evaluating five racemic drugs and their single-enantiomer versions, the Therapeutics Initiative concluded that "[t]he concept that a single enantiomer of a chiral drug may be preferable to a racemic mixture is intellectually appealing. However, in most instances this strategy has not been demonstrated to confer any clinical advantage."[162] Importantly, it was noted that while single-enantiomer drugs may be more effective at the same dosage level, clinical equivalence can be achieved by simply increasing the dosage level of the racemic drug.[163] Courts, however, have not always agreed.[164] Nor is there consensus among commentators, with some suggesting that single enantiomers are clearly better,[165] and others suggesting that even if enantiomers have "clear clinical advantages over racemates" in some cases,[166] the market success of single-enantiomer drugs is really "based more on promotion than on real advantages."[167] Whether the result of marketing or superior properties, the percentage of new drugs that are single enantiomers has increased from 20% to 75% in a recent ten-year period.[168]

¶55 Even if commercial success is due to promotion rather than the merits of the product, a defendant attempting to prove this to the court faces a particularly difficult challenge. On the one hand, it must assert that the enantiomer is not significantly better than the racemate. This is because if the enantiomer were significantly better, this would tend to show that commercial success was due to the superior qualities of the product rather than marketing efforts. Yet if the generic company's assertion is true, then a court will naturally wonder why the generic company has not copied the unpatented racemate rather than the patented enantiomer.[169]

4. No Known or Obvious Process

¶56 Even if a prima facie case of obviousness is established, and no unexpected results can be shown nor favorable secondary considerations relied upon, an enantiomer may nevertheless be nonobvious if no method of resolution is disclosed in or rendered obvious by the prior art. "One of the assumptions underlying a prima facie obviousness rejection based upon a structural relationship between compounds . . . is that a method disclosed for producing one would provide those skilled in the art with a method for producing the other."[170] Due to the fact that enantiomers have identical chemical (but not biological) properties, the process for making the racemate may not make obvious a process for resolving the racemate. Even if the prior art discloses a process for isolating one enantiomer, this process will not necessarily render obvious the process for obtaining the other enantiomer.[171]

> [I]f the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of

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[162] *Do Single Stereoisomer Drugs Provide Value?*, *supra* note 14; Blin, supra note 66, at 625, 627 (concluding that demonstrating improved clinical effectiveness for single-enantiomer drugs over their racemates has proven difficult in most cases).

[163] *Id.*

[164] Ortho-McNeil Pharmaceutical, Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 757 (N.D. W. Va. 2004) ("[T]he evidence reflects a fairly extensive recognition among doctors and hospitals that levofloxacin is not only an effective drug but also is clinically distinguishable from ofloxacin."). Note that levofloxacin was one of the enantiomers evaluated by the Therapeutics Initiative. *Do Single Stereoisomer Drugs Provide Value?*, *supra* note 14.

[165] Agranat et al., *supra* note 58, at 754 ("The debate about the relative merits of racemates and single enantiomers was short lasting, and it was resolved emphatically in favour of the latter."); *see also* Hutt & Valentová, *supra* note 20, at 10 (noting that racemic penicillamine resulted in optic neuritis and was withdrawn from the US market, while the use of D-penicillamine [the single enantiomer] was not observed to cause the adverse side effect; also noting the use of single-enantiomer L-dopa in the treatment of Parkinson's disease resulted in reduced adverse effects as compared to the racemate).

[166] Mansfield et al., *supra* note 20, at 287-88.

[167] *Id.* at 290.

[168] Agranat et al., *supra* note 58, at 753.

[169] *See, e.g.*, *Ortho-McNeil*, 348 F. Supp. 2d at 759 ("Notwithstanding the expiration of the [racemate] patent and [the defendant's] insistence that [the racemate] and [the enantiomer] are virtually indistinguishable, [the defendant] chose to file an NDA only for [the enantiomer].").

[170] *In re* Grose, 592 F.2d 1161, 1168 (C.C.P.A. 1979).

[171] Brenner v. Ladd, 247 F. Supp. 51, 55 (D.D.C. 1965).

a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious. . . .[172]

¶57 Consider this matter from the perspective of motivation to combine and reasonable likelihood of success. The mere disclosure in the prior art of a racemate and a resolution technique does not mean that the given racemate will be amenable to resolution by the given technique. There must be more than a general motivation to resolve a racemate; there must be a motivation to combine particular references with each other. That is, there must be a suggestion from the prior art that a particular racemate can be resolved by a particular technique with a reasonable expectation of success.

CONCLUSION

¶58 Within the law of chemical obviousness, enantiomers present a special case. A disclosed racemate allows one ordinarily skilled in the art to envision the structure of each enantiomer. Given this racemate, the ordinarily skilled worker does not need to select a single molecule from hundreds or thousands of unique molecules that might be imagined by arranging numerous substituents in myriad ways. There are only two species within the genus. The pharmaceutically active racemate is already known to be useful, and the literature is replete with the potential advantages of single-enantiomer drugs over their racemates. One skilled in the art would therefore generally have a motivation to resolve a racemate in the ever-present search for superior pharmaceutical products. True, many single enantiomers have failed to demonstrate improved clinical properties, but while this clearly demonstrates the lack of absolute predictability, it does not necessarily negate a reasonable expectation of success. With advances in separation techniques, the likelihood of success in obtaining a single enantiomer has increased, and the existence of potential benefits has been acknowledged by the FDA's call for single-enantiomer data during the drug approval process. Moreover, the case of enantiomers seems to fall squarely within the circumstances aptly articulated by the Fifth Circuit:

> [W]here a court finds the alleged inventor's work in a field filled with formidable prior art to be no more novel or nonobvious than the conducting of a biological or physiological testing program among catalogued compounds or an easily formulated series of homologues or analogues that logically or predictably should disclose helpful uses, the grant or validation of a patent on the product would be out of keeping with the letter or spirit of the law.[173]

¶59 All of this, of course, is merely a general approach to addressing the patentability of enantiomers. Ultimately "[e]very case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts."[174] Enantiomers may merit patent protection in certain circumstances. For example, if a racemate is disclosed but has no known uses, one skilled in the art would not possess the requisite motivation or likelihood of success. Or if the racemate was disclosed to be highly toxic this could constitute "teaching away" so as to favor nonobviousness. Or perhaps the single enantiomer possesses properties so different in kind or magnitude that they would have been totally unexpected to one skilled in the art.

¶60 Ultimately, the determination of whether and when enantiomers should be patentable is a public policy question and should be addressed with this in mind. Single-enantiomer drugs have in some cases been shown to be superior to their racemates. At the same time "[t]here are . . . financial risks associated with the development of single enantiomers from racemates."[175] To the extent that such

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[172] *In re* Hoeksema, 399 F.2d 269, 274 (C.C.P.A. 1968); *In re* Payne, 606 F.2d 303, 314-15 (C.C.P.A. 1979) ("[T]he presumption of obviousness based on close structural similarity is overcome where the prior art does not disclose or render obvious a method for making the claimed compound."); *In re* Maloney, 411 F.2d 1321, 1323 (C.C.P.A. 1969) ("[T]he presence—or absence—of a suitably operative, obvious process for making a composition of matter may have an ultimate bearing on whether that composition is obvious – or nonobvious – under 35 U.S.C. 103."). *Cf. id.* Emory Univ. v. Glaxo Wellcome Inc., 44 U.S.P.Q.2d 1407, at *9 (N.D. Georgia 1997).

[173] Eli Lilly & Co. v. Generix, 460 F.2d 1096, 1103 (5th Cir. 1972).

[174] *In re* Jones, 958 F.2d 347, 350 (Fed. Cir. 1992).

[175] Hutt & Valentova, *supra* note 20, at 16; Blin, *supra* note 66, at 225 (emphasizing the scientific, administrative, and economic challenges surrounding the commercial development of single enantiomers).

financial risks deter companies from developing single-enantiomer drugs, offering patent protection for those single enantiomers that offer true advantages would both serve the public interest and fulfill the Constitutional objective of promoting the progress of science.

C

Ex parte Bonfils

U.S. Patent and Trademark Office Board of Patent Appeals and Interferences

Appeal No. 2001-2138

Decided February 20, 2002
Released August 27, 2002

PATENTS

1 Practice and procedure in Patent and Trademark Office -- Board of Patent Appeals and Interferences -- Rules and rules practice (§ 110.1105)

Patent examiner who relies on document that is in foreign language bears burden of providing English language translation thereof, at latest, before forwarding appeal to Board of Patent Appeals and Interferences, just as applicant who relies on document in foreign language for rebuttal of rejection must produce English translation in support of his or her position; although examiner and applicants may be able to advance prosecution of case without translation, to extent patentability of claims depends on foreign language reference, record will be incomplete and inadequate until translation has been entered, and in no case should appeal reach board without translation of any foreign language document relied upon by either examiner or applicant.

2 Patentability/Validity -- Obviousness -- Relevant prior art -- Particular inventions (§ 115.0903.03)

There is no per se rule that claimed stereoisomer is obvious in view of disclosure of another stereoisomer in prior art; in present case, patent examiner's rejection of claims for chemical compounds based on disclosure of stereoisomer of claimed compounds in prior art reference is reversed, since there is no evidence in record that ordinary steroid chemist would have expected that enantiomers of prior art compounds would be useful for controlling male fertility in mammals by affecting fertilizing power of spermazoid, as disclosed by applicants, or that said enantiomers would have any particular pharmacological activity.

***1457** Appeal from examiner's rejection of claims in application for patent.

Patent application of Armelle Bonfils and Daniel Philibert, serial no. 08/403,276. [FN1] Applicants appeal from examiner's rejection of claims 1-5 for obviousness pursuant to 35 U.S.C. § 103(a). Reversed.

[Editor's Note: The Board of Patent Appeals and Interferences has indicated that this opinion is not binding precedent of the board.]

Before William F. Smith, administrative patent judge, McKelvey, senior administrative patent judge, and Nagumo, administrative patent judge.

Nagumo, J.

ON BRIEF [FN2]

Decision on appeal under

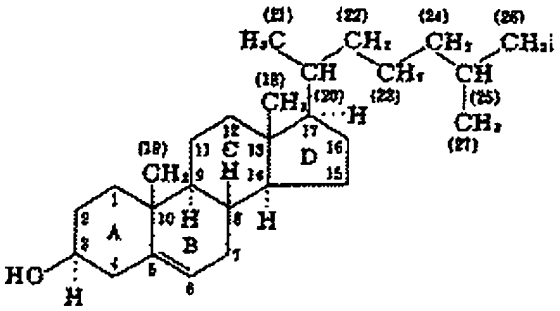
This appeal is from a decision of a primary examiner rejecting claims 1 through 5. Claim 6 has been withdrawn from consideration. We reverse.

A. Findings of fact

Background

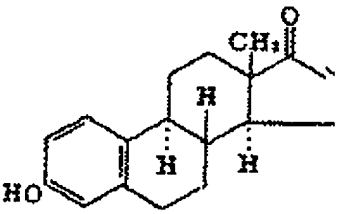
1. Compounds that are mirror images of one another are called "enantiomers." *See In re May*, 574 F.2d 1082, 1085, 197 USPQ 601, 603 (CCPA 1978) for a brief review of stereochemical terminology and conventions. Such compounds are also called "chiral" ('handed'), and "antipodal." (*E.g.*, Brief at 4.)

2. The standard numbering system for steroids is as follows:



(*Louis F. Fieser & Mary Fieser, Steroids* 1 (1959) (" *Fieser*").

3. The naturally occurring steroid estrone has the following stereochemistry:



Estrone

(*Fieser* at 464.)

An atom or group that lies below the plane of the paper is depicted by a dashed line leading to the group, and denoted "&agr;" in the chemical name. An atom or group that lies above the plane of the paper is depicted by a solid line, dark triangles or thickened lines leading to the group, and denoted "&bgr;" in the chemical name. (*May* at 1085, 197 USPQ at 603.) Bonds to atoms or groups that can lie above or below the plane of the paper are denoted by wavy lines. (Spec. at 3, ll.6-9.)

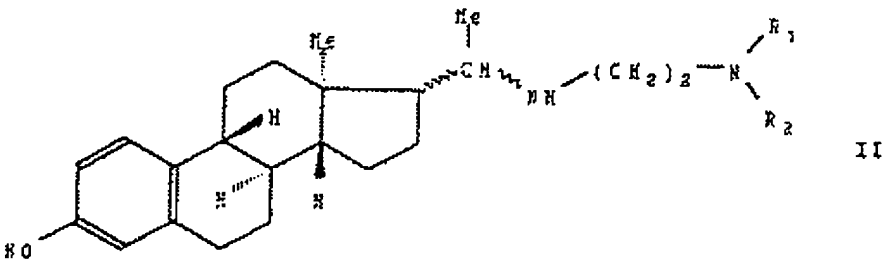
The invention

The record supports the following findings by at least a preponderance of the evidence. [FN3]

4. The invention relates to certain stereoisomers of 20-substituted steroids, and their pharmaceutically acceptable salts. (Spec. at 2.)

***1458** 5. According to Appellants, the compounds are useful for controlling male fertility in mammals *(id.)*, by affecting the fertilizing power of the spermazoid. (Spec. at 14, ll. 16-18.)

6. A preferred compound within the scope of Appellants' invention has the structure shown in formula I':

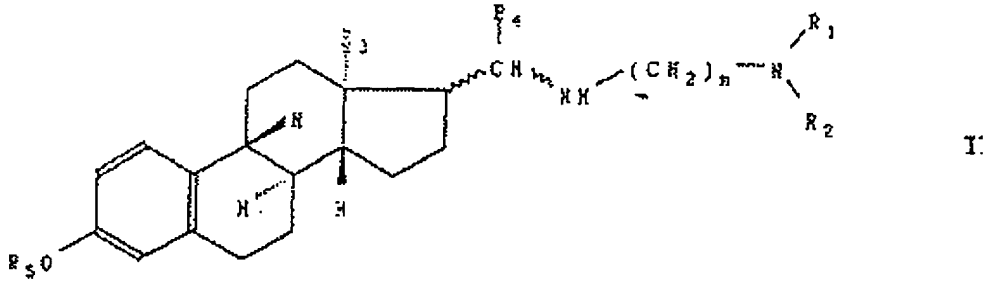


II

where R1 and R2 are methyl.

7. This compound is named (20S) (8&agr; 9&bgr;, 13&agr;, 14&bgr;, 17&agr;) 20-[((dimethylamino)-ethyl)-amino]-19-nor-&Dgr; 1,3,5(10)-pregnatrien-3-ol. (Spec. at 5, II 10-12; claim 5.)

8. Comparison of the structure of formula I' with the structure of naturally occurring estrone shows that Appellants are claiming compounds wherein the B, C, and D fused rings are the mirror image of the naturally occurring estrone ring structure.



I'

wherein R1 and R2 are individually selected from the group consisting of alkyl of 1 to 12 carbon atoms and aralkyl of 7 to 15 carbon atoms or taken together form [sic, from] a saturated heterocycle of 5 to 6 ring members optionally having a second ring heteroatom selected from the group consisting of sulfur, oxygen and nitrogen, R3 is an &agr;-alkyl of 1 to 8 carbon atoms, n is an integer from 2 to 15, R 4 is alkyl of 1 to 12 carbon atoms, R5 is selected from the group consisting of hydrogen, alkyl of 1 to 12 carbon atoms and acyl of an organic carboxylic acid of up to 12 carbon atoms and the wavy lines indicate that the 17- and 20- asymmetrical centers are independent of the absolute R and S configurations and their non-toxic, pharmaceutically acceptable acid addition salts.

The examiner's rejections

10. Claims 1 through 5 were rejected under 35 U.S.C. § 103(a) as being unpatentable over French patent document 1,380,424 ("RU-I"), or French patent document 90,805 ("RU-II"), both assigned to Rousse1-Uclaf. On receipt by the board, no translation for either document was present in the application file.

The claims

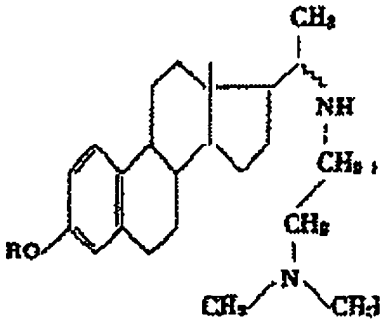
9. Claim 1 is representative and reads as follows:

A compound selected ***1459*** from the group consisting of a compound of the formula

Rousse1-Uclaf I

11. U.S. Patent No. 3,156,619, issued to Bertin and Nedelec on November 10, 1964 ("Bertin"), claims priority in part from RU-I. Although Bertin contains material not included in RU-I, the parallel cites *post* confirm the sense of the French text. We stress that the examiner did not cite Bertin, and that we use it as an informal translation to confirm our reliance on chemical formulas and names disclosed by RU-1.

12. RU-I concerns compounds having the structure:



where R represents hydrogen, a lower alkyl radical, or an acyl radical of a lower organic acid. (Roussel-Uclaf I at 1, left column; Bertin at col. 1, ll. 15-30.)

13. These compounds may be named 3-OR-20-(N,N-dimethylaminoethylamino)-19- nor-&Dgr; 1,2,5(10)-pregnatrienes. (RU-I at 1, right column, ll.5-6; Bertin at col. 2, ll.69-70, and Table I at col. 3 (chemical reaction scheme).)

14. The compounds are disclosed to have antilipemic and hypocholesterolemiantic activities, and to lack any estrogenic activity. (RU-I at 1, left column, second paragraph; Bertin at col. 2, ll.40-43.)

15. The disclosed synthesis of the inventive compounds begins with compounds of formula II, such as 3-OR 20-oxo 19-nor &Dgr;1,3,5(10)-pregnatriene. (RU-1 at 1, left column, last paragraph (see also the chemical scheme on the last page); Bertin at col. 2, ll.49-57.)

RU-II

16. RU-II concerns 11-hydroxy derivatives of the compounds disclosed by RU-I. These are compounds having the same structure as those of RU-1, with a hydroxy (-OH) group attached to the C-ring at the 11-position. (RU-II at 1, left column, lower chemical structure.)

The examiner's rationale

17. In the examiner's words, "[b]oth references teach 20-(&bgr;-N,N-dimethylaminoethyl)amino-19-nor-1,3,5(10)-pregnatrienes having either a hydroxy or an acyl group in the 3-position. (Answer at 3.)

18. The examiner finds that Appellants' claimed subject matter differs from the teachings of the reference by "having a different stereochemistry at the 8, 9, 13 and 14 positions." (*Id.* at 4.)

19. The examiner then observes that "the claimed compounds are stereoisomers of the compounds taught by the references." (*Id.*)

20. The examiner concludes that "[i]n the absence of unobvious results, a single isomer of a compound would be obvious to one having ordinary skill in the art." (*Id.*)

21. The examiner argues that the evidence of unexpected results presented by Appellants is unpersuasive because they did not provide side-to-side comparisons of the new enantiomer and the known enantiomer. Hence, according to the examiner, Appellants have not shown that "the two isomers would have different properties or that the claimed compounds have some unexpected or superior property." (*Id.*)

Appellant's argument

22. In response to the first office action on the merits of the application rejecting claims 1-5 over RU-II, Appellants enclosed a copy of RU-I and stated:

"the compounds disclosed in the references have the normal stereochemistry of the ***1460** pregnane derivatives which is 8&bgr; 9&agr; 13&bgr; 14&agr; and in contrast thereto, the compounds of Applicants' invention have the *unusual* antipodal configuration of 8&agr; 9&bgr; 13&agr; 14&bgr;. This unnatural configuration of the steroids of Applicants' invention is obtained by a process in which the starting compound is the antipodal (-)-estrone

(8&agr; 9&bgr; 13&agr; 14&bgr;), whereas, the prior art compounds start with the natural (k)-estrone (8&bgr; 9&agr; 13&bgr; 14&agr;) in the reaction sequence. [Paper No. 7 at 2, emphasis original.]

23. Appellants argue that the references relied on by the Examiner do not teach Appellants' specific 8&agr;, 9&bgr;, 13&agr;, 14&bgr; configuration of steroids. (Brief at 3.)

24. Appellants also argue that the references fail because they do not enable those of ordinary skill in the art to make the claimed antipodal compounds. (*Id.* at 3-4.)

25. Appellants argue further that evidence of record (Crossley [FN4]) shows that the pharmaceutical activity of a new single stereoisomeric form "is not obvious to envisage" compared to a known stereoisomeric form or a known racemic mixture. (Brief at 4.)

26. Appellants urge that one skilled in the art would not have been able to predict the discovered effect on spermazoid levels based on the known antilipemic activity of the reference compounds. (*Id.*)

27. Appellants conclude that the obviousness rejection fails.

B. Discussion

We shall not sustain the examiner's rejection, which is based on an inadequate evidentiary record, and which fails to establish a prima facie case of unpatentability.

The evidentiary record

Findings of fact and conclusions of law by the USPTO must be made in accordance with the Administrative Procedure Act, 5 U.S.C. § 706(A), (E) (1994). Zurko v. Dickinson , 527 U.S. 150, 158, 119 S.Ct. 1816, 1821, 50 USPQ2d 1930, 1934 (1999). Our reviewing court has held that findings of fact must be supported by substantial evidence within the record. In re Gartside , 203 F.3d 1305, 1315, 53 USPQ2d 1769, 1775 (Fed. Cir. 2000) ("Because our review of the Board's decision is confined to the factual record compiled by the Board . . . the 'substantial evidence' standard is appropriate for our review of Board factfindings. *See* 5 U.S.C. § 706(2)(E).") In the present case, the absence of English translations of the French documents is a serious gap in the evidentiary record.

The examiner has relied on two French patent documents as evidence of unpatentability. In this case, it appears that Appellants have not been disadvantaged in responding to the rejections, as they provided the documents [FN5] and are French nationals. Thus, we may presume they reviewed and understood the French-language documents. In reviewing the record presented on appeal, however, we cannot say the same of ourselves. If we were to rely strictly on the documents of record, we would be unable to make adequate factual findings regarding the teachings of the French language references, and what they would have meant to one of ordinary skill in the art. Thus, we would be unable to explain the evidentiary basis for our holding of affirmance or reversal. This alone is sufficient basis for reversal or remand.

1 When the examiner, as here, relies on a document that is in a foreign language, the examiner bears the burden of providing an English translation, at the latest, before forwarding the appeal to the board. Similarly, when the Applicant relies on a document that is in a foreign language for rebuttal of a rejection, the Applicant bears the burden of producing an English translation to support his position. In the past, the board has often expended the resources necessary to obtain a translation of a foreign language patent or technical article. When it did so, however, the burden of examining the claims with respect to that translation fell on the board in the first instance. Moreover, to the extent that the board relies on parts of a translation not previously provided to an applicant, any affirmance generally has to be a new ground of rejection under 37 CFR § 1.196(b)--which can result in further prosecution. Clearly, this procedure is inefficient and wastes the time and resources of the USPTO and Appellants.

Efficient prosecution dictates that, when a rejection (or rebuttal) is founded on a document that is not in English, a translation be provided as soon as possible. When, as here, the Applicants can read and understand the ***1461** reference, and when there appears to be no dispute about what the reference teaches, reliance on a translation provided to the board along with the examiner's Answer may not merit a new ground of rejection. When the Applicants or their representatives cannot read the non-English language, however, they may not be able to form an adequate understanding of the reference to rebut the rejection on the merits or to amend the claims to avoid the reference. In such cases, Applicants should insist that the examiner provide a translation before a final rejection is entered, seeking supervisory intervention if necessary. By the same token, if Applicants rely on a foreign language reference to rebut a rejection, the examiner may insist on a translation as a condition of a complete response, just as a declaration submitted in a foreign language, without a certified translation, would have no weight. We do not encourage *pro forma* objections: in some cases, the examiner and Applicants may be able to advance prosecution of a case without a translation. To the extent that the patentability of claims depends on a foreign language reference, however, the record will be incomplete and inadequate until a translation has been entered. In no case should an appeal reach the board without a translation of any foreign language reference relied on by either the examiner or the Applicant.

In this case, unusual circumstances, described in the next section, permit an immediate resolution of this appeal.

The prima facie case of obviousness

In the following discussion, we shall refer only to RU-1, as the examiner and Appellants appear to treat them cumulatively, and because Bertin, a patent in the same "family" that claims priority, in part, on RU-1, provides some guidance. We feel this is a reasonable way to proceed because the examiner and Appellants do not appear to have disputed their characterizations of the references. Only the inferences and conclusions each draws from the references are in dispute.

The burden is on the examiner to establish a *prima facie* case of obviousness of the claimed subject matter over prior art references. In re Deuel , 51 F.3d 1552, 1557, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995). Only after that burden is met must the applicant come forward with arguments or evidence in rebuttal. *Id.* Findings of fact must be supported by substantial evidence in the record. In re Gartside , 203 F.3d 1305, 1315, 53 USPQ2d 1769, 1775 (Fed. Cir. 2000). A rejection under § 103 is proper only when "the PTO establishes that the invention as claimed in the application is obvious over cited prior art, *based on the specific comparison of that prior art with claim limitations." In re Ochiai*, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995) (emphasis added).

The only fact relied on by the examiner in this appeal is that RU-1 discloses a stereoisomer of the claimed compounds. (*See* the Answer at 4; the final office action on the merits, Paper No. 12 at 2-3; and the first office action on the merits, Paper No. 8 at 3.) While a single disclosed chemical structure or formula might suffice as the *sole* evidence of unpatentability in a rejection under 35 U.S.C. § 102 for anticipation, such will rarely, if ever, suffice as substantial evidence of obviousness under § 103(a). This is because the examiner must explain why the differences would have been obvious, and the explanation must be supported by evidence in the record.

2 In the present case, the examiner appears to have relied on a *per se* rule that a stereoisomer is obvious in view of a disclosure of another stereoisomer in the prior art. (Answer at 4.) This is error. *Ochiai* at 1572, 37 USPQ2d at 1133 ("reliance on *per se* rules of obviousness is legally incorrect and must cease.") Moreover, the cases cited by the examiner (Paper No. 8 at 3) do not support the examiner's position.

In the most recent case relied on by the examiner, In re Deuel , 51 F.3d 1552, 34 USPQ2d 1210 (Fed.

Cir. 1995), the court explained that a *prima facie* case of obviousness based on structural similarity *may* arise *if* the "[s]tructural relations provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* at 1558, 34 USPQ2d at 1214. The court stressed that "[i]n the case before us there must be adequate support in the prior art for the. . .change in structure, in order to complete the PTO's *prima facie* case and shift the burden of going forward to the applicant." *Id., quoting In re Grabiak*, 769 F.2d, 729, 731-32, 226 USPQ 870, 872 (Fed. Cir. 1985). *See also, e.g., In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979) ("An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art ***1462** to make a claimed compound, in the expectation that compounds similar in structure will have similar properties."); *May*, 574 F.2d at 1094, 197 USPQ at 611 ("the basis of the prima facie case of obviousness, at least to a major extent, is based on the presumed expectation that compounds which are similar in structure will have similar properties."). Nothing in these cases supports the examiner's apparent position that the disclosure of one enantiomer is sufficient by itself to establish *a prima facie* case of obviousness of the other enantiomer. Where, as here, there is evidence of unpredictability (*e.g.*, Crossley), and no evidence of common pharmaceutical or biological properties [FN6] , the "presumed expectation" of similar properties due to the similar structures is not well-founded.

Examination of the remaining cases cited by the examiner shows that words that might be interpreted as establishing a *prima facie* case of obviousness of a claimed stereoisomer over the enantiomer disclosed in the prior art are either *dicta* because they were not necessary for the disposition of the case, or they were made within the context of the record before the court, and are thus of limited general applicability.

In In re Adamson , 275 F.2d 952, 125 USPQ 233 (CCPA 1960) the court upheld an obviousness rejection of claims to "[a] laevo-isomer of a compound . . . substantially separated from the dextro-isomer" over references disclosing the racemate, i.e., a mixture of equal amounts of the enantiomers. More specifically, the references disclosed synthetically produced compounds of the same formula claimed. A chemistry text taught that synthetically produced substances containing asymmetric carbon atoms responsible for optical activity are optically inactive due to the formation of equal amounts of the laevo- and dextro-isomers. *Adamson* at 953, 125 USPQ at 234. Adamson argued that the invention was patentable because they discovered that the prior art product was a racemate, i.e., comprised of optical isomers, that the isomers could be separated, and that there were unexpected results. The court rejected the first two arguments, finding that, in view of the textbook, one of ordinary skill in the art would have recognized the reference product to be a racemate, and would also know how to separate the isomers. *Id.* at 954-55, 125 USPQ at 235. Finally, the court found the evidence of unexpected results was not persuasive, and so affirmed the rejection. Because the court did not rely on the general proposition that one optical isomer is *prima facie* obvious over its enantiomer, *Adamson* does not stand for that proposition.

In Brenner v. Ladd , 247 F.Supp. 51, 147 USPQ 87 (D.D.C. 1965), the district court agreed that, "in the absence of unexpected or unobvious beneficial properties, an optically active isomer is unpatentable over either the isomer of opposite rotation or, as in this case, the racemic compound itself." *Id.* at 56, 147 USPQ at 91. The court's decision, however, appears to be based on its factual finding that the only disclosed utility for the compounds L-acl or L-acl.HCL was their use as intermediates in the production of L-lysine. *Id.* The court held, however, that this utility would have been obvious over a prior art teaching that DL-acl (the racemate) could be hydrolyzed to DL-lysine through the intermediate DL-acl.HCI. *Id.* In modern terminology, the court found that the only evidence of record showed that L-acl had similar properties to the

known DL-acl, and held that the evidence supported a *prima facie* case of obviousness. The broad proposition is thus mere *dicta*, as it was unnecessary for the court's decision.

In In re Anthony , 414 F.2d 1383, 162 USPQ 594 (CCPA 1969), Anthony conceded a *prima facie* case of obviousness of the claims to d-and l-enantiomers over a prior art teaching of the racemate. *Id.* at 1386, 162 USPQ at 596. Thus, the issue was not in controversy, and the court's statements, which are limited to reporting the course of proceedings below, are *dicta*.

The examiner has not directed our attention to any evidence in the record that the ordinary steroid chemist would have expected that the enantiomers of the RU-1 compounds would have affected spermazoid activity, as disclosed by Appellants, or that the enantiomers would have any particular common pharmacological properties. Thus, the examiner has not shown that RU-1 provides any suggestion to make or use the claimed enantiomers. Accordingly, we reverse this rejection.

Appellants appear to urge that the failure of RU-1 to teach any utility for the claimed compounds, and the known unpredictable nature of the changes in activity, toxicity, and utility due to changes in chirality, require reversal of ***1463** the examiner's rejection. (Brief at 4.) To the extent that Appellants intend to argue that the examiner has not established any basis for concluding that one of ordinary skill in the art would have had a reasonable expectation that the claimed compounds would have similar biological properties as the reference compounds, we agree that a *prima facie* case of obviousness has not been established, and that the rejection must be reversed for this reason as well.

Further considerations

In the event of further prosecution, the examiner and Appellants should consider the following issues:

Information disclosure statement

The information disclosure statement filed April 3, 1995, in Paper No. 3, has not been initialed by the examiner, although the examiner checked a box on the first action, Paper No. 6, indicating that the Notice of Art Cited by Applicant, form PTO-1449, was attached to the action. The examiner should take appropriate action.

Potential new matter issues:

The examiner and Appellants should determine whether new matter has been entered into the specification in violation of 35 U.S.C. § 132. Appellants submitted amendments to the specification (Paper No. 10, at page 1), alleging that certain material was omitted due to an error of translation from their French priority document. (*Id.*, at page 3.) However, the foreign priority document does not appear to be incorporated by reference into Appellants' specification. Under 35 U.S.C. § 119, the benefit of priority is granted only to the extent that "the same application would have if filed in this country on the date on which the application for patent for the same invention was first filed in such foreign country," i.e., to the extent that common subject matter is disclosed. Absent an explicit incorporation by reference, the foreign priority document is not available as antecedent basis for amendments to the specification or claims. Ex parte Bondiou , 132 USPQ 356, 358 (Bd. App. 1961) (changing disclosure from "four hours" to--four days--not permitted because it introduced new matter under 35 U.S.C. § 132); *see also* MPEP § 2163.07 (8th Ed., August 2001). The examiner and Appellants should determine whether support for the amendments exists in the specification as filed. *See In re Oda*, 443 F.2d 1200, 1205-06, 170 USPQ 268, 272 (CCPA 1971) (permitting corrections of translation errors, explaining that the amendments did not result in any change in the claimed subject matter, and that the evidence of record was sufficient to show that one skilled in the art would have appreciated not only the existence of error, but what the error was and how to correct it).

In claim 3, the definition of "n" appears to be superfluous because n does not appear in formula I'.

In claim 5, a left parenthesis appears to be missing in the bracketed portion of the chemical name:

20-[((dimethylamino)-ethyl)-amino] . . ..

C. Decision

The rejections are *reversed.*

D. Order

Upon consideration of the appeal, and solely for the reasons given, it is ORDERED that the decision of the examiner rejecting claims 1 through 5 is *reversed.*

FURTHER ORDERED that no time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED

FN1. Application for patent filed March 13, 1995. Appellants claim priority under 35 U.S.C. § 119 to April 1, 1994, based on an application filed in France. The real party in interest is Roussel Uclaf, of Paris, France (Brief, Paper No. 18, at 1.)

FN2. Appellants, through counsel, requested an oral hearing. (Paper No. 20, filed May 6, 1998.)Our review of the case revealed that a hearing was not necessary to assist us in the resolution of the issues on appeal.

FN3. To the extent these findings of fact discuss legal issues, they may be treated as conclusions of law.

FN4. Roger Crossley, *The Relevance of Chirality to the Study of Biological Activity*, 48 *Tetrahedron* 8155, 8156, 8174, 8175 (1992), filed attached to Paper No. 14 on November 12, 1997.

FN5. RU-1 was filed with Paper No. 7 on August 1, 1996; RU-2 was filed with Paper No. 3 on April 3, 1995.

FN6. We stress the absence of evidence predicting pharmaceutical or biological properties of the compounds because it is only in interactions with other chiral molecules that the properties of one enantiomer will differ from its mirror image: all properties of the enantiomers that involve interactions only with achiral molecules will be identical, by symmetry.

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